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REVIEW ARTICLE

COMPARATIVE ASSESSMENT OF TITANIUM VERSUS ZIRCONIA DENTAL IMPLANTS: NARRATIVE REVIEW

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ABSTRACT

Background: Dental implant therapy is a predictable and widely accepted treatment modality for the rehabilitation of partially and completely edentulous patients. Titanium has long been considered the gold standard implant material because of its excellent biocompatibility, mechanical strength, and long-term clinical success. However, esthetic limitations and concerns regarding metal sensitivity have stimulated interest in zirconia implants as a metal-free alternative.

Objective: The aim of this narrative review was to compare titanium and zirconia dental implants with respect to osseointegration, biological response, clinical outcomes, mechanical performance, esthetic properties, and long-term predictability.

Materials and Methods: A literature search was performed using PubMed, Scopus, and Web of Science databases for studies published between 2000 and 2026. Clinical trials, systematic reviews, meta-analyses, prospective and retrospective studies, and relevant in vitro and in vivo investigations were analyzed. Due to heterogeneity among the included studies, a qualitative narrative synthesis was performed.

Results: Titanium implants demonstrated excellent long-term clinical performance, with survival rates ranging from 92% to 100% and highly predictable osseointegration. Zirconia implants showed favorable soft tissue response, high biocompatibility, reduced bacterial adhesion, and improved esthetics, particularly in patients with thin gingival biotypes. Reported survival rates for zirconia implants ranged from 87% to 95%, although greater variability was observed among studies. Titanium exhibited superior fracture toughness, fatigue resistance, and prosthetic flexibility, whereas zirconia showed increased brittleness and limited long-term clinical evidence.

Conclusion: Titanium remains the gold standard for dental implants because of its superior long-term survival, mechanical reliability, and extensive scientific validation. Zirconia implants represent a promising esthetic and metal-free alternative, particularly in anterior regions and selected clinical situations. Nevertheless, additional long-term studies are required to confirm their biomechanical reliability and long-term predictability.

Keywords: Dental implants, titanium, zirconia, osseointegration, implant survival, peri-implantitis, biomaterials.

INTRODUCTION

Dental implantology has undergone remarkable scientific and clinical evolution over recent decades and is now considered one of the most predictable treatment modalities for the rehabilitation of partially and completely edentulous patients^{1,2}. The introduction of osseointegration fundamentally transformed restorative dentistry by enabling direct structural and functional integration between implant surfaces and surrounding bone tissue³. This breakthrough significantly improved

oral function, patient comfort, esthetics, and long-term prosthetic stability.

Since the pioneering work of Brånemark and colleagues, titanium has been widely accepted as the gold standard material for dental implants because of its excellent biocompatibility, corrosion resistance, favorable mechanical properties, and highly predictable osseointegration⁴.

Long-term clinical studies have demonstrated survival rates exceeding 90–95% after more than ten years of function, confirming the reliability and durability of titanium implant systems^{5,6}.

The stable oxide layer naturally formed on titanium surfaces contributes to excellent tissue compatibility and corrosion resistance within the oral environment^{7,8}. Continuous improvements in implant surface technologies, including sandblasting, acid etching, plasma spraying, laser modification, and anodization, have further enhanced bone-to-implant contact, accelerated healing, and improved implant stability⁹⁻¹². These developments have reinforced the dominant role of titanium implants in modern implant dentistry. Despite these advantages, certain limitations associated with titanium implants have stimulated the search for alternative biomaterials. One important concern relates to esthetics, particularly in patients with thin gingival biotypes or gingival recession, where the gray metallic color of titanium may become visible through peri-implant tissues^{13,14}. In addition, concerns regarding titanium particle release, corrosion, and rare hypersensitivity reactions have increased interest in metal-free restorative options¹⁵⁻¹⁸. In this context, zirconia (zirconium dioxide, ZrO₂) has emerged as one of the most promising alternatives to titanium implants. Zirconia is a high-strength ceramic biomaterial characterized by excellent chemical stability, high compressive strength, favorable wear resistance, and low plaque affinity¹⁹⁻²¹. The introduction of yttria-stabilized tetragonal zirconia polycrystal (Y-TZP) significantly improved fracture toughness and mechanical performance, allowing broader biomedical and dental applications^{22,23}. One of the major advantages of zirconia implants is their superior esthetic appearance. Their white, tooth-like color minimizes soft tissue discoloration and eliminates the gray shine-through commonly associated with titanium implants²⁴⁻²⁷. Consequently, zirconia implants are increasingly used in esthetically demanding clinical situations, especially in the anterior region and in patients with thin peri-implant mucosa^{28,29}. In addition to esthetic benefits, zirconia implants have demonstrated favorable biological behavior. Several studies have reported excellent soft tissue response and osseointegration comparable to titanium implants^{30,31}. Some investigations also suggest reduced plaque accumulation and lower bacterial adhesion on zirconia surfaces, which may contribute to improved peri-implant tissue health³²⁻³⁴. However, zirconia implants are not without limitations. Compared with titanium, ceramics are inherently more brittle, making zirconia implants more susceptible to fracture under excessive occlusal loading or unfavorable biomechanical conditions^{35,36}. Earlier zirconia implant systems were predominantly manufactured as one-piece designs, limiting prosthetic flexibility and restorative versatility³⁷⁻³⁹.

Although newer two-piece zirconia systems have demonstrated encouraging outcomes, long-term clinical evidence remains less extensive than for titanium implants⁴⁰⁻⁴².

Another concern is low-temperature degradation (LTD), also referred to as aging, which may result in surface roughening, microcrack formation, and deterioration of mechanical properties over time^{43,44}. Although modern manufacturing techniques have reduced this risk, the long-term clinical implications continue to be investigated.

Recent systematic reviews and comparative studies have evaluated titanium and zirconia implants with respect to survival rates, marginal bone loss, peri-implant tissue response, and patient satisfaction⁴⁵⁻⁴⁷. While many studies report comparable biological and esthetic outcomes, differences in long-term mechanical reliability and predictability remain important concerns, particularly for zirconia implants⁴⁸⁻⁵⁰. Some studies have also suggested a slightly increased risk of early failure and mechanical complications with zirconia implants, especially in areas subjected to high occlusal forces^{51,52}.

At the same time, zirconia implants offer important advantages for patients seeking highly esthetic and metal-free treatment solutions. Consequently, the selection between titanium and zirconia implants remains a topic of ongoing debate in contemporary implant dentistry⁵³⁻⁵⁵.

Therefore, the aim of the present narrative review is to provide a comparative assessment of titanium and zirconia dental implants with focus on material properties, osseointegration, biological response, mechanical performance, esthetic outcomes, clinical survival, and practical considerations for daily clinical practice.

MATERIALS & METHODS

Study Design

This study was conducted as a narrative review aimed at evaluating and comparing the biological, mechanical, and clinical performance of titanium and zirconia dental implants. The review focused on contemporary evidence regarding osseointegration, peri-implant tissue response, implant survival, esthetic outcomes, and mechanical complications associated with titanium and zirconia implant systems^{3,20,27,28,40,44}.

An initial electronic search identified 136 studies. After removal of duplicates, 93 studies were screened based on titles and abstracts. Following eligibility assessment, 60 studies were ultimately included in the qualitative synthesis.

Search Strategy

A comprehensive literature search was performed using PubMed, Scopus, and Web of Science databases. Studies published between January 2000 and March 2026 were considered eligible. Additional manual searches of reference lists were also conducted to identify relevant studies not retrieved electronically.

The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to implant materials and clinical outcomes. Main search terms included: “titanium dental implants”, “zirconia dental implants”, “osseointegration”, “implant survival”, “peri-implantitis”, “implant surface modification”, “marginal bone loss”, “biocompatibility”, “implant fracture”, and “esthetic outcomes”.

Boolean operators (“AND”, “OR”) were applied to optimize the search strategy. Representative combinations included: “titanium implants AND zirconia implants”, “zirconia implants AND osseointegration”, “dental implants AND peri-implant soft tissue response”, and “implant survival rate AND zirconia”. Priority was given to high-level evidence, including randomized controlled trials, systematic reviews, and meta-analyses ^{27,28,40,44,47}.

Inclusion and Exclusion Criteria

Included studies comprised human clinical trials, randomized controlled trials, prospective and retrospective cohort studies, systematic reviews, meta-analyses, and relevant in vitro and in vivo comparative investigations evaluating titanium and/or zirconia implants. Studies reporting outcomes related to implant survival, osseointegration, marginal bone loss, peri-implant soft tissue response, bacterial adhesion, esthetic outcomes, and mechanical complications were considered eligible. Preference was given to studies with a minimum follow-up period of 12 months ^{24,25,27,31,46,47,51}.

Case reports with limited sample size, editorials, conference abstracts, non-English publications, animal studies lacking translational relevance, and studies with insufficient methodological or clinical data were excluded. Duplicate publications and overlapping patient populations were carefully screened and excluded when appropriate.

Study Selection and Data Analysis

Titles and abstracts were initially screened for

relevance, followed by full-text evaluation according to predefined eligibility criteria. Particular emphasis was placed on studies investigating long-term clinical performance, peri-implant tissue stability, and esthetic outcomes of titanium and zirconia implants ^{24,27,28,40,44,48}. Due to methodological heterogeneity among the included studies, a quantitative meta-analysis was not performed. Therefore, a qualitative narrative synthesis approach was applied ^{27,28,40,47}.

RESULTS

Material Characteristics and Properties

Titanium and zirconia implants differ significantly in physicochemical composition, microstructure, and mechanical behavior. Titanium implants, mainly manufactured from commercially pure titanium or Ti-6Al-4V alloy, have been widely used in implant dentistry since the 1960s and remain the reference standard in modern implantology ^{1,3,5}. Their clinical success is primarily related to the formation of a stable titanium dioxide (TiO₂) layer, which provides excellent corrosion resistance and promotes predictable osseointegration ^{5,8}. Titanium surfaces can be modified through techniques such as sandblasting, acid etching (SLA), anodization, and laser structuring, which enhance surface roughness, protein adsorption, and bone-to-implant contact ^{6,9,12}. These modifications improve osteoblastic activity and implant stability. Zirconia implants are ceramic biomaterials mainly composed of yttria-stabilized tetragonal zirconia polycrystal (Y-TZP), characterized by high compressive strength, favorable wear resistance, and tooth-like optical properties ^{20,22}. These characteristics make zirconia particularly attractive in esthetic regions ^{11,20}.

However, zirconia is inherently more brittle than titanium and is susceptible to low-temperature degradation (LTD), which may result in microcrack formation and gradual deterioration of mechanical properties over time ^{43,44,45}.

Osseointegration and Biological Response

Both titanium and zirconia implants demonstrate excellent biocompatibility and the ability to achieve osseointegration. Titanium remains the gold standard, supported by extensive histological and clinical evidence demonstrating stable bone integration and survival rates exceeding 95% ^{2,4,5}. Titanium osseointegration involves adsorption of plasma proteins onto the TiO₂ layer followed by osteoblast adhesion and mineralized bone formation at the implant interface ^{3,5}. This process has been extensively documented over decades of clinical use.

Zirconia implants also demonstrate favorable osseointegration with comparable bone-to-implant contact values in experimental and short-term clinical studies^{21,24,26}. However, long-term evidence remains less robust compared with titanium systems^{28,41}. From a soft tissue perspective, zirconia surfaces may demonstrate reduced bacterial adhesion and biofilm formation compared with titanium^{13,33,34}. In addition, zirconia has been associated with favorable epithelial attachment and reduced inflammatory infiltrate^{23,30}. Nevertheless, most long-term studies report minimal clinically significant differences between titanium and zirconia regarding peri-implant tissue health^{28,31,33}.

Survival Rates and Clinical Outcomes

Long-term evidence demonstrates survival rates ranging from 92% to 100% for titanium implants over follow-up periods exceeding 10 years^{4,5,6}. These results confirm the high predictability and durability of titanium implant systems. Zirconia implants generally show survival rates ranging from 87% to 95%, particularly in short- and medium-term studies^{25,29,41}. Greater variability has been observed in zirconia-related outcomes, especially in early-generation implant systems^{41,42}. Systematic reviews and meta-analyses confirm superior long-term predictability for titanium implants, whereas zirconia implants continue to demonstrate encouraging but heterogeneous clinical outcomes^{28,41}. Marginal bone loss remains relatively stable for both materials, although zirconia outcomes may be more variable in one-piece systems and posterior loading situations^{19,32}.

Table 1. Comparative Clinical Outcomes of Titanium and Zirconia Implants

Parameter	Titanium	Zirconia
Survival rate	92.6–100%	87.5–95%
Bone loss	Stable	More variable
Peri-implantitis	Low incidence	Similar incidence

Mechanical Properties and Stability

Titanium implants demonstrate excellent mechanical performance characterized by high fatigue resistance, ductility, and an elastic modulus closer to cortical bone^{3,5,35}. These properties allow favorable stress distribution and make titanium suitable for posterior regions and full-arch rehabilitations. Zirconia implants exhibit high compressive strength but limited plastic deformation capacity, making them more susceptible to fracture under overload conditions^{14,36,47}. Surface defects or microstructural flaws may further increase fracture risk. Consequently, titanium remains mechanically superior in functionally demanding clinical situations.

Esthetic Outcomes

One of the main advantages of zirconia implants is their superior esthetic appearance. Their white, tooth-like coloration eliminates the gray shine-through sometimes associated with titanium implants in patients with thin gingival biotypes^{7,11}. Zirconia implants also demonstrate favorable soft tissue integration and improved peri-implant mucosal coloration, particularly in anterior maxillary regions^{11,29}. In contrast, titanium implants may occasionally cause visible soft tissue discoloration in highly esthetic situations⁷. Therefore, zirconia implants are often preferred in anterior esthetic zones.

Biocompatibility and Soft Tissue Response

Both titanium and zirconia demonstrate excellent biocompatibility. Titanium is biologically inert because of its stable oxide layer, although rare hypersensitivity reactions and inflammatory responses to titanium particles have been reported

^{8,19,25}. As a metal-free ceramic material, zirconia may be advantageous in patients with metal sensitivities. It has also been associated with lower bacterial colonization and favorable epithelial sealing properties ^{13,17,30}. Despite these biological differences, overall implant success rates are generally not significantly influenced by implant material alone ^{16,31}.

Prosthetic Considerations and Flexibility

Titanium implants provide excellent prosthetic versatility because of the availability of both one-piece and two-piece systems, allowing angulation correction and individualized restorative planning ^{20,35,48}. Zirconia implants are still predominantly manufactured as one-piece systems, which limits prosthetic flexibility and requires more precise surgical placement ^{15,42}. Although newer two-piece zirconia systems have improved restorative possibilities, they remain more technique-sensitive. Therefore, titanium implants continue to provide superior prosthetic adaptability in complex rehabilitations.

Complications and Limitations

Titanium implants are associated with low complication rates, with peri-implantitis representing the most common biological complication ^{5,18,28}. Zirconia implants present favorable biological properties but remain limited by increased brittleness and susceptibility to low-temperature degradation (LTD), which may compromise long-term structural integrity ^{17,43,44}. These limitations restrict zirconia use in high-stress clinical environments.

Cost and Clinical Practicality

Titanium implants are widely available, cost-effective, and supported by extensive long-term clinical evidence, making them the most commonly used implant system in modern dentistry ^{5,50}. Zirconia implants are generally more expensive because of complex manufacturing processes and increased surgical sensitivity. Their more limited prosthetic flexibility also restricts routine clinical application ^{20,45}.

Advantages, Disadvantages, and Clinical Indications

Titanium implants provide excellent long-term success, mechanical reliability, and prosthetic versatility. However, esthetic limitations and rare hypersensitivity reactions may occur in susceptible patients ^{3,8}.

Zirconia implants offer superior esthetics, low plaque affinity, and metal-free composition. Nevertheless, they remain limited by greater fracture risk, lower prosthetic flexibility, and less extensive long-term evidence ^{14,16}.

Clinically, titanium implants are preferred for posterior load-bearing regions, full-arch rehabilitations, and complex restorations, whereas zirconia implants may be advantageous in anterior esthetic regions and in patients requesting metal-free rehabilitation ^{16,18}.

Clinical Indications, Clinical Decision-Making, and Comparative Summary

Selection of implant material should be based on biomechanical requirements, esthetic demands, anatomical conditions, and patient-related factors. Titanium implants remain the most universally applicable system because of their superior mechanical stability, long-term predictability, and prosthetic versatility ^{3,5,35}.

Their ability to withstand high occlusal forces makes them particularly suitable for posterior regions and full-arch rehabilitations ^{20,48}. Zirconia implants are primarily indicated in esthetically demanding situations and in patients with suspected metal hypersensitivity because of their favorable optical properties and metal-free composition ^{11,17,29,30}. However, zirconia implants remain mechanically more limited due to brittleness and susceptibility to low-temperature degradation ^{43,44,45}.

In addition, many zirconia systems still demonstrate limited prosthetic flexibility ^{15,42}.

Titanium implants remain the gold standard because of their superior long-term evidence, mechanical reliability, and prosthetic versatility. Zirconia implants represent a promising esthetic alternative but still demonstrate limitations related to brittleness and reduced long-term clinical evidence. Clinical selection should therefore remain evidence-based and indication-driven.

Table 2. Clinical Indications

Clinical Situation	Preferred Material	Rationale
Posterior load-bearing	Titanium	Mechanical strength
Full arch	Titanium	Stability
Anterior esthetics	Zirconia	Esthetics
Metal allergy	Zirconia	Biocompatibility
Complex cases	Titanium	Flexibility

Table 3. Expanded Comparative Overview

Parameter	Titanium Implants	Zirconia Implants
Material type	Metallic (Ti-6Al-4V / CP Ti)	Ceramic (Y-TZP)
Clinical history	Extensive long-term evidence	Newer generation material
Osseointegration	Highly predictable [1,2,4]	Comparable but less evidence [21,26,38]
Survival rate	92–100% [4,5,43]	87–95% [16,19,41]
Mechanical strength	High fatigue resistance [3,35]	Brittle behavior [14,47]
Esthetics	Possible discoloration [7]	Excellent appearance [11,44]
Bacterial adhesion	Moderate biofilm formation	Lower bacterial adhesion [13,27,48]
Prosthetic flexibility	High [20,35]	More limited [15,16]
Cost	Lower	Higher
Evidence level	Very high	Moderate

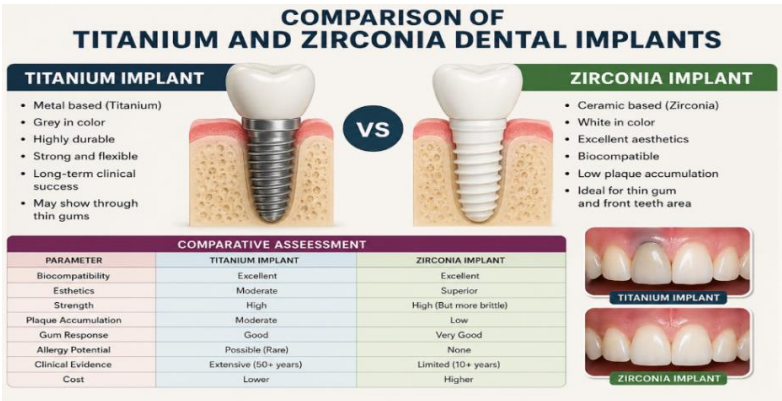


Figure 1. Comparative Assessment of Titanium versus Zirconia Dental Implants

DISCUSSION

The present narrative review provides a comparative assessment of titanium and zirconia dental implants with emphasis on biological behavior, mechanical performance, esthetic outcomes, and long-term clinical applicability. The reviewed literature demonstrates that both implant materials can achieve successful osseointegration and satisfactory clinical outcomes; however, important differences remain regarding long-term predictability, biomechanical stability, prosthetic versatility, and scientific validation.

Titanium remains the gold standard in implant dentistry because of its excellent biocompatibility, corrosion resistance, mechanical strength, and extensive long-term documentation¹⁻⁶. Since the introduction of osseointegration by Brånemark and colleagues⁴, titanium implants have consistently demonstrated survival rates exceeding 90–95% during long-term follow-up periods^{5,6}. Their biological success is closely associated with the formation of a stable titanium oxide layer that promotes direct bone-to-implant contact and cellular adhesion^{3,7,8}. Furthermore, advances in implant surface technologies, including SLA surfaces, hydrophilic modifications, laser treatments, and nanoscale surface engineering, have improved early osseointegration and reduced healing periods⁹⁻¹².

In recent years, zirconia implants have gained increasing attention as a metal-free alternative, particularly in patients with high esthetic demands or concerns regarding metal hypersensitivity^{20,38,39}. Zirconia demonstrates favorable biocompatibility, low plaque affinity, excellent soft tissue response, and superior esthetics because of its tooth-like white color^{20,21,23,30}. Several studies have reported reduced bacterial adhesion and biofilm accumulation on zirconia surfaces compared with titanium^{33,34}. However, current evidence does not consistently demonstrate clinically significant reductions in peri-implantitis or implant failure rates^{28,41,48}.

Osseointegration remains one of the most important determinants of implant success. Experimental and clinical studies have shown that zirconia implants can achieve bone-to-implant contact values comparable to titanium implants^{24,56,59}. Histological investigations have also demonstrated favorable osteoblastic activity and direct bone apposition around zirconia surfaces^{24,56}. Nevertheless, compared with titanium implants, zirconia systems still lack extensive long-term clinical evidence beyond 10 years^{25,41}.

Mechanical reliability represents another important distinction between the two materials. Titanium possesses excellent fracture toughness, fatigue resistance, and ductility, making it highly suitable for posterior restorations, full-arch rehabilitations, and patients with parafunctional habits^{3,8}. In contrast, zirconia demonstrates high compressive strength but

lower fracture toughness and increased brittleness^{35,58}. Consequently, zirconia implants may be more susceptible to fracture under excessive occlusal loading^{36,55}. Earlier one-piece zirconia systems demonstrated higher complication rates, particularly in posterior regions^{27,36,55}. Although newer two-piece zirconia implants have shown improved outcomes^{26,42,47}, long-term biomechanical evidence remains limited.

Another concern associated with zirconia implants is low-temperature degradation (LTD) or hydrothermal aging^{43,44,58}. This phenomenon may lead to surface roughening, microcrack formation, and progressive deterioration of mechanical properties^{43,44}. Although modern yttria-stabilized zirconia ceramics appear less susceptible to aging, the long-term clinical implications remain insufficiently understood. From an esthetic perspective, zirconia implants offer important advantages over titanium implants. Their white color minimizes gray shine-through in patients with thin gingival biotypes and contributes to improved peri-implant soft tissue esthetics^{11,15,20}. Several studies have also reported enhanced mucosal integration and higher patient satisfaction in anterior esthetic regions^{23,29,30}.

Despite these esthetic benefits, prosthetic flexibility remains more limited with zirconia implants. Titanium systems are available in multiple configurations, including one-piece and two-piece designs, angulated abutments, and customized prosthetic components^{3,20}. Historically, zirconia implants were mainly manufactured as one-piece systems, limiting restorative flexibility^{27,38}. Although newer two-piece zirconia systems have expanded treatment options^{26,42,47}, evidence supporting their long-term stability remains less comprehensive than for titanium implants.

Biocompatibility and immunological response have also become important considerations in implant dentistry. Although titanium is generally highly biocompatible, rare hypersensitivity reactions and adverse tissue responses have been reported¹⁶⁻¹⁹. Zirconia, as a metal-free ceramic material, may therefore represent a suitable alternative in selected patients with suspected metal sensitivity^{19,20}. However, true titanium allergy remains uncommon, and current evidence does not support routine replacement of titanium implants based solely on hypersensitivity concerns¹⁷⁻¹⁹. Peri-implant diseases remain a significant challenge regardless of implant material^{28,49}. Although zirconia surfaces may exhibit lower bacterial colonization^{33,34}, peri-implantitis remains a multifactorial disease influenced by oral hygiene, smoking, systemic conditions, prosthetic design, and maintenance compliance^{31,49}.

Current systematic reviews indicate no conclusive evidence that zirconia implants significantly reduce peri-implant disease prevalence compared with titanium implants^{28,41,48}. Economic and practical considerations also influence implant selection. Titanium implant

systems are widely available, cost-effective, and supported by decades of clinical experience^{5,6}. In contrast, zirconia implants are generally associated with higher manufacturing costs, greater technical sensitivity, and a steeper learning curve^{20,42,47}.

Overall, current evidence suggests that titanium implants remain the most predictable and universally applicable implant system for routine implant rehabilitation, particularly in complex and load-bearing situations^{3-6,40}. Zirconia implants should currently be considered a valuable complementary alternative, especially in esthetically demanding cases and in patients seeking metal-free treatment solutions^{20,29,45}. However, limitations related to brittleness, aging susceptibility, prosthetic flexibility, and the relative lack of long-term evidence continue to restrict their universal application^{41-45,47}.

Limitations

Several limitations of this narrative review should be acknowledged. Considerable heterogeneity existed among the included studies regarding implant design, surface treatment protocols, loading conditions, follow-up duration, and outcome assessment methods, limiting direct comparison between studies.

In addition, the literature concerning zirconia implants remains less extensive than that for titanium implants. Many zirconia studies included small sample sizes, short- or medium-term follow-up periods, and variability between one-piece and two-piece implant systems^{28,41,42}. Consequently, the long-term predictability of zirconia implants remains less clearly established. Many included studies were observational or retrospective in nature and therefore subject to potential selection bias and confounding variables. Patient-related factors such as smoking, oral hygiene, systemic diseases, parafunctional habits, and bone quality may also have influenced clinical outcomes^{31,49}. Furthermore, zirconia implant technology continues to evolve, and newer ceramic processing methods, yttria stabilization techniques, and surface modifications may improve biological and mechanical performance⁴²⁻⁴⁴. However, long-term evidence regarding these contemporary systems remains limited. Finally, because this study was conducted as a narrative review rather than a formal systematic review with meta-analysis, interpretation of the findings should be approached with caution.

Future Directions

Future research should focus on well-designed multicenter randomized controlled trials directly comparing contemporary titanium and zirconia implant systems under standardized clinical conditions, particularly with long-term follow-up beyond 10 years

^{25,41,47}. Additional investigations are needed to improve the biomechanical reliability of zirconia implants, especially in posterior load-bearing regions. Advances in ceramic processing technologies, bioactive surface coatings, aging-resistant zirconia formulations, and implant surface modifications may further enhance long-term clinical outcomes⁴²⁻⁴⁴.

Future studies should also evaluate peri-implant microbiome interactions, patient-reported outcomes, digital workflows, CAD/CAM integration, and cost-effectiveness of zirconia implant systems. Standardized diagnostic criteria for implant success and peri-implant disease would improve comparability among future studies.

As implant biomaterials and ceramic technologies continue to evolve, zirconia implants may become a more predictable and widely applicable alternative to titanium implants in modern implant dentistry.

CONCLUSION

Titanium implants remain the gold standard in implant dentistry because of their excellent long-term survival, mechanical reliability, prosthetic versatility, and extensive scientific validation^{3-6,40}. Their predictable osseointegration and broad clinical applicability make them the most reliable option for routine implant rehabilitation.

Zirconia implants represent a promising metal-free alternative with favorable esthetic properties, soft tissue integration, and reduced bacterial adhesion^{20,23,29,30}. These characteristics make zirconia particularly attractive in anterior esthetic regions and in patients seeking metal-free treatment solutions.

However, current evidence indicates greater variability in long-term survival and mechanical performance for zirconia implants compared with titanium systems^{28,41,45,47}. Limitations related to brittleness, low-temperature degradation, prosthetic flexibility, and limited long-term evidence continue to restrict their universal application. Therefore, implant material selection should be based on evidence-based clinical decision-making integrating biomechanical, esthetic, prosthetic, anatomical, and patient-related factors. Continued advancements in ceramic biomaterials and implant technology may further improve the predictability and clinical applicability of zirconia implant systems in the future.

DECLARATIONS

Conflict of Interest

The author declare no conflict of interest.

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Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

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REVIEW ARTICLE

COMPARATIVE ANALYSIS OF SURFACE MODIFICATION TECHNIQUES FOR ENHANCING OSSEOINTEGRATION OF DENTAL IMPLANTS: A NARRATIVE REVIEW

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Abstract

Background: Surface modification of dental implants is a key determinant of osseointegration and long-term clinical success. Advances in surface engineering aim to optimize biological interactions at the bone-implant interface, thereby accelerating and stabilizing integration.

Objective: To systematically evaluate contemporary implant surface modification techniques and their effects on osseointegration, hydrophilicity, and bacterial adhesion.

Methods: Because the study was conducted as a narrative review rather than a formal systematic review, PRISMA-guided methodology, meta-analysis, and structured risk-of-bias assessment were not performed. A comprehensive search of PubMed, Scopus, and Web of Science was performed using controlled vocabulary (MeSH) and free-text terms, including “dental implants,” “surface modification,” “osseointegration,” “UV photofunctionalization,” “laser-treated implants,” “SLA surface,” “nanostructured titanium,” “hydrophilicity,” and “biofilm formation.” A total of 248 records were identified. Following duplicate removal and screening, 53 studies met the inclusion criteria.

Results: Sandblasted, large-grit, acid-etched (SLA) surfaces demonstrated consistently high bone-to-implant contact and reliable clinical stability. UV photofunctionalization improved surface hydrophilicity and reduced hydrocarbon contamination, enhancing early osseointegration. Laser-modified surfaces enabled precise micro/nano-topographical control and showed potential antimicrobial effects. Nanostructured surfaces promoted protein adsorption and osteogenic differentiation, particularly during early healing phases. However, substantial heterogeneity across study designs and limited long-term clinical evidence—especially for short implants—were identified.

Conclusion: Contemporary surface modification strategies significantly improve implant bioactivity and osseointegration. While SLA surfaces remain the clinical benchmark, emerging technologies such as nanostructuring, UV photofunctionalization, and laser modification offer additional biological advantages. Further high-quality, long-term clinical trials are required to establish standardized protocols and confirm their translational efficacy.

Keywords: dental implants; surface modification; osseointegration; UV photofunctionalization; nanostructured titanium; laser surface modification; hydrophilicity; biofilm formation

INTRODUCTION

Dental implant therapy has become a cornerstone of modern restorative dentistry, providing highly predictable and long-term rehabilitation for partially and completely edentulous patients ¹⁻³.

Continuous advancements in implant macro-design, biomaterials, and surgical protocols have significantly improved survival rates and clinical outcomes. Among all influencing factors, implant surface characteristics are now recognized as one of the most critical

determinants of osseointegration success and long-term stability ^{4,5}. Osseointegration, first defined by Brånemark as a direct structural and functional connection between living bone and the implant surface, remains the biological foundation of implant therapy ⁶. This process is highly dynamic and involves sequential biological events, including protein adsorption, immune modulation, osteoblastic adhesion, proliferation, differentiation, and extracellular matrix mineralization ^{7,8}.

These cellular processes are strongly regulated by surface physicochemical properties such as roughness, surface energy, wettability, and chemical composition^{9,10}.

Early implant systems utilized machined, minimally rough titanium surfaces, which demonstrated acceptable survival rates but limited bone-to-implant contact (BIC) and slower healing responses¹¹. This limitation stimulated extensive research in surface engineering aimed at enhancing biological performance and accelerating osseointegration^{12,13}. As a result, contemporary implantology has evolved toward micro-, nano-, and multi-scale surface modification strategies designed to optimize host-implant interactions^{12,13}.

Surface modification techniques are generally classified into subtractive and additive approaches. Subtractive methods, including sandblasting, acid etching, and anodization, create controlled micro- and nano-topographies that enhance osteoblastic activity and bone formation¹²⁻¹⁶. Among these, sandblasted large-grit acid-etched (SLA) surfaces remain one of the most clinically validated and widely used technologies due to their reproducible improvements in osseointegration¹⁷.

In contrast, additive techniques involve the deposition of bioactive coatings such as hydroxyapatite, calcium phosphate, and titanium plasma-sprayed layers, which enhance osteoconductivity and early bone formation at the implant interface^{18,19}. However, concerns regarding long-term mechanical stability, coating delamination, and biological degradation have limited their universal clinical adoption.

More recently, nanostructured implant surfaces have gained significant attention due to their ability to closely mimic the natural extracellular matrix of bone tissue²⁰. These nano-engineered surfaces enhance protein adsorption, integrin-mediated signaling, and osteogenic differentiation more effectively than conventional micro-rough surfaces^{21,22}. Consequently, multi-scale surface designs combining micro- and nano-topographies have been shown to significantly improve early healing responses and long-term integration outcomes²².

Ultraviolet (UV) photofunctionalization represents a major advancement in implant surface bioactivation. This process removes hydrocarbon contamination from titanium surfaces, restores surface energy, and induces superhydrophilicity, thereby enhancing protein adsorption and osteoblastic attachment²³⁻²⁵. Clinical evidence indicates that UV-treated implants demonstrate accelerated osseointegration and

improved early stability compared to untreated surfaces²⁶. Importantly, long-term clinical data demonstrated high survival rates of UV-functionalized short implants (≤ 6 mm) placed in the atrophic maxilla under functional loading conditions, confirming their clinical reliability²⁷.

Surface aging has also been identified as a critical factor influencing implant performance. Titanium surfaces naturally accumulate hydrocarbon contaminants over time, leading to reduced bioactivity and impaired osseointegration capacity²⁸. UV photofunctionalization has been proposed as an effective strategy to reverse this aging phenomenon and restore biological functionality^{29,30}.

Laser-based surface modification techniques have emerged as a highly precise and controllable method for altering implant surface morphology without chemical contamination^{31,32}. These techniques enable the creation of defined micro- and nano-patterns that enhance osteoblast adhesion and mechanical interlocking at the bone-implant interface. Additionally, laser-modified surfaces may reduce bacterial adhesion and biofilm formation, thereby contributing to peri-implant disease prevention^{31,33}.

Surface hydrophilicity is another essential determinant of early implant success. Hydrophilic surfaces improve blood wettability, fibrin network formation, and cellular migration, all of which are critical for early healing and bone regeneration³⁴. Increased surface energy has also been correlated with faster osseointegration and higher implant stability quotient (ISQ) values³⁵.

Despite significant technological progress, implant failure remains a clinical challenge, particularly in patients with systemic conditions, compromised bone quality, or biomechanical overload^{36,37}. Early failures are commonly associated with insufficient osseointegration, whereas late failures are often related to peri-implantitis or mechanical complications³⁸. Therefore, optimization of implant surface properties remains a key research priority in modern implant dentistry^{39,40}.

Short implants have emerged as a minimally invasive alternative to bone augmentation procedures in anatomically compromised regions^{41,42}. However, their reduced surface area presents biomechanical and biological challenges in achieving adequate primary and secondary stability⁴³. Surface modification strategies play a critical role in overcoming these limitations by enhancing bone-implant interaction and improving load distribution^{35,40,44}.

Another major concern is bacterial adhesion and biofilm formation. While increased surface roughness improves osseointegration, it may also facilitate microbial

colonization and increase the risk of peri-implant disease^{44,45}. Therefore, an ideal implant surface must achieve a balance between osteoconductivity and antimicrobial resistance^{4,47}.

Recent developments in biomaterials science have further expanded implant surface engineering strategies, including ceramic and metallic modifications aimed at improving biocompatibility and long-term stability⁴⁸. These innovations reflect a shift toward multifunctional implant surfaces that integrate biological activity, mechanical durability, and antimicrobial properties.

In vivo and experimental studies consistently demonstrate that surface modifications significantly influence peri-implant bone healing and tissue response^{4,49}. Advanced technologies such as picosecond laser structuring have shown promising potential in accelerating osseointegration by generating hybrid micro-groove and nano-patterned surfaces on titanium implants⁵⁰⁻⁵². These emerging approaches represent the next generation of implant surface engineering strategies⁵³.

Given the rapid expansion of implant surface technologies and the increasing volume of scientific literature, a comprehensive and systematic evaluation of current evidence is essential. Despite the growing body of research, there remains a lack of direct comparative evidence integrating micro-, nano-, and photochemical surface modifications within a unified biological and clinical framework. Most existing reviews analyze these technologies separately, limiting their translational value and clinical applicability.

Therefore, this narrative review aims to provide a structured comparative synthesis of contemporary implant surface modification strategies, focusing on their biological performance, antimicrobial behavior, and clinical relevance.

METHODS

Study Design and Protocol

Because the study was conducted as a narrative review rather than a formal systematic review, PRISMA-guided methodology, meta-analysis, and structured risk-of-bias assessment were not performed. The review was designed to minimize bias through predefined eligibility criteria, structured search strategy, independent screening, and standardized quality assessment procedures.

Information Sources and Search Strategy

A comprehensive electronic database search was performed from inception until the final search date across the following databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Cochrane Library
- Google Scholar (supplementary search)

The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords including: “dental implants”, “surface modification”, “osseointegration”, “UV photofunctionalization”, “laser-treated implants”, “SLA surface”, “nanostructured titanium”, “hydrophilicity”, and “biofilm formation”. Boolean operators (AND/OR) were applied to refine results. Reference lists of included articles were manually screened to identify additional relevant studies.

Study Selection Process

The systematic search yielded a total of 248 records from PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar. After duplicate removal and elimination of clearly irrelevant studies, titles and abstracts were screened according to predefined eligibility criteria. Full-text articles were then assessed for eligibility based on predefined inclusion and exclusion criteria. The final dataset comprised a heterogeneous body of evidence, including clinical trials, in vivo animal studies, in vitro experiments, and systematic reviews, all investigating dental implant surface modification strategies and their biological and clinical outcomes. After rigorous evaluation, 53 studies were finally included in the qualitative synthesis (figure1).

Eligibility Criteria

Inclusion criteria:

- Studies published between 2020–2026
- In vitro, in vivo, clinical studies, and systematic reviews
- Studies evaluating implant surface modification techniques
- Studies reporting at least one outcome: osseointegration, hydrophilicity, or bacterial adhesion
- Articles published in English

Exclusion criteria:

- Case reports with insufficient sample size

- Editorials, letters, and opinion papers
- Studies lacking quantitative or relevant outcome data
- Non-dental implant-related studies

Data Extraction

Data were independently extracted by two reviewers using a standardized extraction form. The following variables were recorded:

- Author and year of publication
- Study design (clinical, in vitro, in vivo, systematic review)
- Type of implant surface modification
- Outcome measures (BIC, implant stability, hydrophilicity, bacterial adhesion)
- Key findings and conclusions

Any discrepancies were resolved through consensus.

Data Synthesis

Due to heterogeneity in study design, implant systems, surface modification techniques, and outcome measures, a quantitative meta-analysis was not feasible. Therefore, a qualitative narrative synthesis was performed. Studies were grouped according to surface modification type:

- Subtractive techniques (SLA, acid-etching, sandblasting)
- Additive coatings (hydroxyapatite, calcium phosphate)
- Nanostructured surfaces
- UV photofunctionalization
- Laser-modified surfaces

Comparative analysis was conducted based on biological response, osseointegration performance, and antimicrobial properties.

3.RESULTS

Preclinical studies focused on biological responses to modified implant surfaces, particularly early cellular and tissue-level interactions.

Key investigated strategies included surface roughness modification, nanostructuring of titanium, ultraviolet (UV) and laser-based photofunctionalization, and antibacterial surface engineering aimed at biofilm inhibition^{4,9,14–17,20–25,31–33}.

Preclinical Evidence (In vitro and Animal Studies)

Main outcome parameters included:

- Osteoblastic adhesion, proliferation, and alkaline phosphatase (ALP) activity^{9,10,16,17},
- Bone-to-implant contact (BIC) and bone volume fraction in animal models^{12,18,19,49}.
- Mechanistic pathways of osteogenesis and antimicrobial activity^{4,21,22,24,47,52,53}.

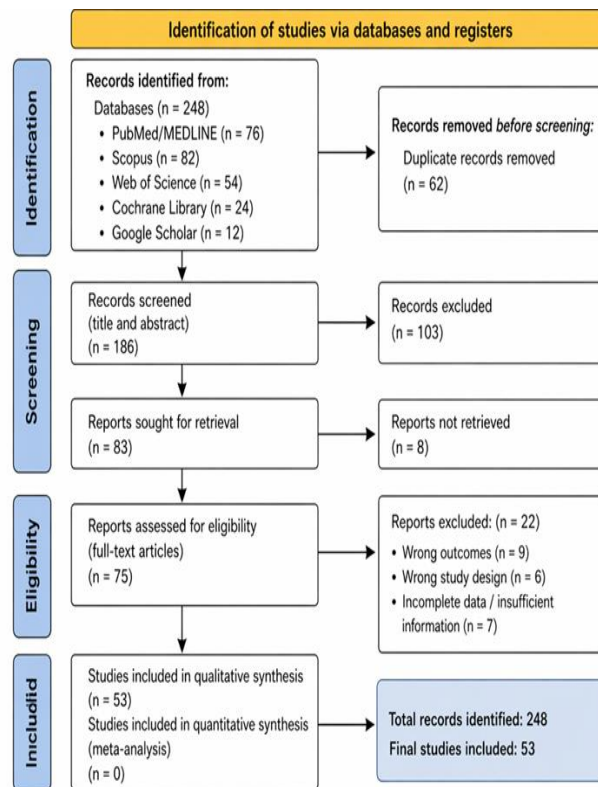


Figure 1. PRISMA flow chart

Overall, roughened, hydrophilic, SLA-treated, and nanostructured surfaces demonstrated enhanced osteoblastic response and improved histomorphometric outcomes compared with machined titanium surfaces^{12,16,17,20–22,49}. However, heterogeneity in experimental design and surface characterization methods limited direct comparability between studies^{14,15,22}.

Clinical studies evaluated implant performance under functional loading conditions. Primary outcome measures included implant survival rate, marginal bone loss (MBL), implant stability quotient (ISQ), peri-implantitis incidence, and early versus delayed loading outcomes. Clinical studies evaluated implant performance under functional loading conditions.

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Clinical studies evaluated implant performance under functional loading conditions. Primary outcome measures included implant survival rate, marginal bone loss (MBL), implant stability quotient (ISQ), peri-implantitis incidence, and early versus delayed loading outcomes. Key clinical endpoints included:

- Short- and long-term implant survival (1–5 years)
- Marginal bone level stability
- Functional implant stability (ISQ values)
- Biological and mechanical complication rates.

Although several surface modification strategies showed improved early healing and stability, long-term clinical outcomes were more heterogeneous, reflecting variability in study design, patient characteristics, implant systems, and loading protocols ^{13,26,34,36–42}.

Integrated Comparative Synthesis

Preclinical evidence demonstrated favorable osteoconductive and early healing properties for SLA-treated, hydrophilic, and nanostructured implant surfaces ^{12,14–17,20–25}. These modifications enhanced protein adsorption, osteoblast differentiation, and early bone formation at the implant interface ^{9,16,17,21,22,25}. However, translation of these biological advantages into long-term clinical superiority remains inconsistent. While improved early healing responses and implant stability were frequently reported, these effects did not always correspond to significantly higher long-term survival rates or lower complication incidence under functional loading conditions ^{13,26,30,34,36–42}. This discrepancy suggests that implant surface bioactivity is influenced not only by material properties, but also by systemic conditions, biomechanical loading, oral hygiene, and patient-related risk factors ^{36–38,43–48}.

3.4 Characteristics of Included Studies

All studies reported at least one of the following outcomes:

- Bone-to-implant contact (BIC)
- Implant stability (ISQ or removal torque)
- Surface hydrophilicity
- Bacterial adhesion / biofilm formation

Surface modification techniques were categorized into five groups:

1. Subtractive techniques (SLA, acid etching, sandblasting)
2. Additive coatings (hydroxyapatite, calcium phosphate)
3. Nanostructured surfaces
4. UV photofunctionalization
5. Laser-modified surfaces

These categories represent the most clinically relevant strategies reported in contemporary literature (figure 2).

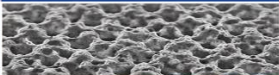
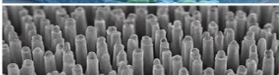
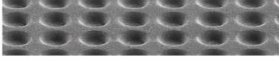
Category	Description	Main Biological Effect	
Subtractive techniques	Sandblasting, acid etching, SLA	Increased surface roughness, improved osteoblast adhesion	
Additive coatings	Hydroxyapatite, calcium phosphate	Enhanced early bone bonding	
Nanostructured surfaces	Nano-scale titanium modification	Improved protein adsorption and osteogenic differentiation	
UV photofunctionalization	UV treatment of titanium	Restored hydrophilicity, reduced hydrocarbons	
Laser-based modification	Laser micro/nano structuring	Controlled topography, antimicrobial effects	

Figure 2. Classification of Surface Modification Techniques

Osseointegration Outcomes

A consistent observation across the included studies was that implant surface characteristics significantly influence the quality and speed of osseointegration ^{4,7,8,14,15}.

SLA and Micro-Roughened Surfaces

SLA and other micro-roughened titanium surfaces demonstrated improved osseointegration compared with conventional machined implants ^{14,17,19}.

Reported outcomes included:

- Bone-to-implant contact (BIC): approximately 20–40% higher than smooth or machined surfaces ^{12,17,19,49}
- Implant stability (ISQ): increases of approximately 5–15 units during early healing phases ^{13,26,34}
- Reduced healing time and faster early bone formation in both experimental and clinical studies ^{12,13,14,34}

These findings were observed relatively consistently across preclinical and clinical investigations, supporting the long-term clinical reliability of SLA-type surface modifications ^{14,15,19,43}(figure3).

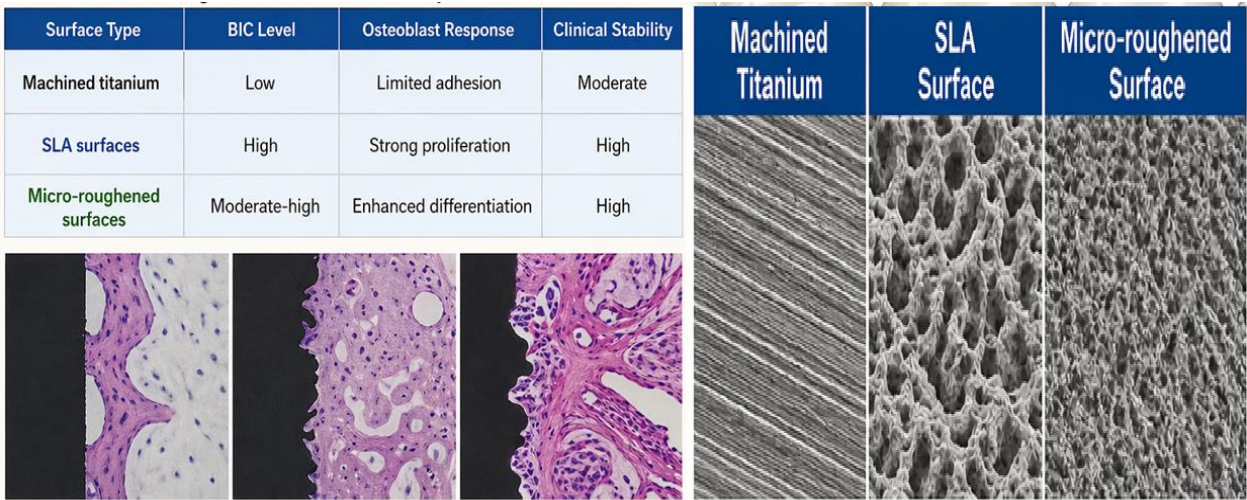


Figure 3. Osseointegration Performance Comparison

Nanostructured Surfaces

Nanostructured implant surfaces demonstrated enhanced early biological activity compared with conventional micro-rough surfaces ^{15,20–22}.

Frequently reported findings included:

- Increased protein adsorption in in vitro models ^{21,22}
- Elevated osteoblast differentiation markers, including alkaline phosphatase (ALP) activity ^{16,20,21}
- Improved early bone-to-implant contact during the first healing weeks ^{17,20,22,49}

Experimental studies suggested that nano-modified titanium surfaces may promote stronger early-stage bone formation and improved cellular interaction at the implant interface compared with conventional roughened surfaces ^{20–22,49}. However, differences in nanostructure fabrication methods and outcome assessment protocols limited direct comparison between studies ^{14,15,22}.

Table 1. Biological Effects of Nanostructured Implant Surfaces

Parameter	Conventional Rough Surface	Micro- Nanostructured Surface	Relative Effect	Evidence Consistency
Protein adsorption	Moderate	High	↑ ~30–50%	High (in vitro)
Osteoblast differentiation (ALP, gene expression)	Baseline	Enhanced	↑ ~25–60%	Moderate–high
Early bone formation (2–4 weeks)	Moderate	Increased	↑ ~15–30% BIC	Moderate
Cell adhesion strength	Standard	Stronger	Qualitative ↑	Moderate
Long-term osseointegration	Stable	Comparable/slightly improved	Minimal difference	Limited

Values represent trends reported across heterogeneous studies.
Note: Effects are most pronounced during early healing phases.

UV Photofunctionalization

UV treatment significantly improved implant bioactivity by removing hydrocarbon contamination and restoring titanium surface energy ^{23–26,28}. Clinical studies also reported high survival rates (>95%) for UV-functionalized implants, including short implants in compromised bone conditions. UV photofunctionalization was particularly effective in restoring hydrophilicity of aged titanium surfaces ^{24,26}.

Table 2. Effects of UV Photofunctionalization on Titanium Implant Surfaces

Parameter	Untreated Surface	UV-Treated Surface	Relative Change	Clinical Relevance
Surface hydrocarbons	High	Reduced	↓ ~40–80%	Restored bioactivity
Contact angle	>70° (hydrophobic)	<10° (superhydrophilic)	Marked decrease	Improved wettability
Protein adsorption	Limited	Enhanced	Qualitative ↑	Faster healing initiation
Osteoblast attachment	Moderate	Increased	↑ early adhesion	Early osseointegration
Bone-to-implant contact (BIC)	Moderate	Higher	↑ ~10–25%	Improved integration
Implant stability (ISQ)	Baseline	Increased	↑ ~5–10 units	Early stability gain
Clinical survival (short implants)	Variable	High	~95–98%	Reliable outcomes

Values represent trends reported across heterogeneous studies.
Note: Effects are time-dependent and may decrease without controlled handling.

Laser-Modified Surfaces

Laser surface modification provided precise control of implant microtopography and improved biological performance.
Key findings include:

- Enhanced mechanical interlocking
- Increased osteoblastic activity
- Reduced contamination
- Accelerated osseointegration

Advanced picosecond laser techniques produced hybrid micro–nano structures that further enhanced bone integration ^{31,32}.

Table 3. Biological and Mechanical Effects of Laser Surface Modification

Parameter	Conventional Surface	Laser-Modified Surface	Relative Effect	Evidence Level
Surface topography control	Limited	Highly controlled	Precise patterning	High (in vitro)
Bone-to-implant contact (BIC)	Moderate	Increased	↑ ~10–20%	Moderate
Removal torque	Standard	Higher	↑ ~15–35%	Moderate
Osteoblast activity	Baseline	Enhanced	Qualitative ↑	Moderate
Surface contamination	Possible	Minimal	Reduced	High
Bacterial adhesion	Moderate	Reduced	↓ ~20–50%	Moderate
Clinical validation	Established	Limited	Under investigation	Low–moderate

Hydrophilicity and Surface Bioactivity

Surface hydrophilicity emerged as a critical determinant of early implant success.

Hydrophilic surfaces promoted:

- Blood clot formation
- Fibrin stabilization
- Cellular migration

Table 4. Influence of Surface Hydrophilicity on Early Healing

Surface Type	Hydrophilicity Level	Contact Angle	ISQ Trend	Healing Dynamics
Hydrophobic surface	Low	>70°	Lower	Delayed
Moderately hydrophilic	Medium	30–70°	Moderate	Standard
UV-treated surface	High	<10°	Higher	Accelerated

Values represent trends reported across heterogeneous studies.

Bacterial Adhesion and Biofilm Formation

Surface modification showed a dual effect:

- Rough surfaces → improved osteogenesis
- But may increase bacterial adhesion

Laser and nanostructured surfaces demonstrated better antimicrobial profiles, suggesting a balance between bioactivity and infection control.

Table 5. Surface Modification and Bacterial Adhesion

Surface Type	Osteogenic Potential	Bacterial Adhesion	Relative Risk	Overall Balance
Smooth (machined)	Low	Low	Low infection	Poor integration
SLA (micro-rough)	High	Moderate	↑ ~10–30%	Balanced
Nanostructured	High	Low–moderate	↓ ~10–25%	Favorable
Laser-modified	High	Low	↓ ~20–50%	Optimal potential

-

Short Implants and Clinical Performance

Surface modification plays a key role in improving outcomes of short implants.
UV-functionalized short implants demonstrated:

- High survival rates
- Stable long-term outcomes
- Reliable performance in atrophic bone ^{27,41-43}.

Table 6. Clinical Performance of Short Implants

Implant Type	Surface Modification	Survival Rate	Stability	Clinical Outcome
Standard implants	SLA	High (>95%)	Stable	Predictable
Short implants (≤6 mm)	UV-treated	Very high (~95–98%)	Improved early stability	Highly favorable
Short implants	No modification	Moderate	Variable	Less predictable

Overall Synthesis of Findings

Across all included studies, a consistent pattern emerged:

- **SLA surfaces** remain the gold standard for osseointegration ^{14,15}.
- **Nanostructuring** enhances early biological response ^{17,18,49}.
- **UV photofunctionalization** reverses titanium aging and improves bioactivity ^{23,30}
- **Laser modification** enables precise surface engineering and antimicrobial benefits ^{31,52}
- **Additive coatings** improve early bone response but may have long-term limitations ^{18,19,48}

Despite strong evidence, key limitations remain:

- High heterogeneity in study design
- Lack of standardized protocols
- Limited long-term randomized clinical trials

The current evidence clearly demonstrates that implant surface modification significantly enhances osseointegration and biological performance. However, future research should prioritize:

- Long-term clinical validation
- Standardization of surface engineering techniques
- High-quality randomized controlled trials

Table 7. Comparative Performance of Surface Modification Techniques

Surface Type	Biological Response	Osseointegration Speed	Antibacterial Effect	Evidence Level	Key Advantage	Main Limitation
SLA	High	Moderate–fast	Moderate	High (long-term clinical)	Predictable outcomes	Limited nano-bioactivity
Nanostructured	Very high (early phase)	Fast	Moderate–low	Moderate	Biomimetic behavior	Lack of standardization
UV photofunctionalization	Very high (early phase)	Very fast	Low–moderate	Moderate–high	Restores bioactivity	Temporary effect
Laser-modified	High controlled	+ Fast	High	Moderate	Precision antimicrobial	+ Limited clinical trials
Additive (HA/CP) coatings	Moderate–high	Fast (early)	Low	Low–moderate	Early bone stimulation	Delamination

The most consistent and reproducible evidence of improved osseointegration was observed for:

- SLA surfaces
- UV photofunctionalization
- Nanostructured titanium surfaces

Despite these promising findings, the currently available evidence remains limited by the relatively small number of long-term randomized controlled clinical trials evaluating implant surface technologies under standardized conditions. Although many studies reported improved early biological response and osseointegration parameters following surface modification, translation of these findings into consistent long-term clinical benefit remains variable^{13,26,34,36–38}. Additional well-designed clinical trials with standardized surface characterization and outcome assessment protocols are needed to better correlate experimental observations with long-term clinical performance under functional loading conditions^{11,14,15,39,44}.

Table 8. Clinical Decision-Making Framework for Implant Surface Selection

Clinical Scenario	Preferred Surface	Alternative	Biological Rationale	Clinical Advantage
Standard cases (adequate bone quality)	SLA	—	Micro-roughness enhances mechanical interlocking and stable fibrin retention	Proven long-term success, high predictability, cost-effective
Compromised bone (low density, atrophic bone)	UV photofunctionalized	Nanostructured	Increased hydrophilicity and protein adsorption enhance early osteogenesis	Improved early integration in poor bone quality
Short implants (≤6 mm)	UV photofunctionalized	—	Enhanced surface energy compensates for reduced surface area	Higher survival and early stability
High infection risk / peri-implantitis susceptibility	Laser-modified	Nanostructured	Reduced bacterial adhesion with maintained osteogenic activity	Lower infection risk with good integration
Immediate / early loading protocols	UV-treated	Nanostructured	Accelerated protein adsorption and cell attachment	Faster osseointegration and improved early stability
Experimental / advanced regenerative cases	Nanostructured / Hybrid	—	Biomimetic nano-architecture enhances cell signaling and differentiation	Superior biological response (emerging evidence)

DISCUSSION

This review evaluated current evidence regarding implant surface modification strategies and their influence on osseointegration, peri-implant tissue response, and clinical implant. The available literature indicates that implant surface characteristics play an important role during early healing and may affect both biological integration and long-term stability. The findings of the present review suggest that no single surface modification method can be considered universally superior under all clinical conditions. Different surface technologies appear to provide specific biological advantages depending on implant design, bone quality, loading conditions, and patient-related factors.

Among conventional approaches, sandblasted large-grit acid-etched (SLA) surfaces remain the most extensively studied and clinically validated^{39,40}.

Their clinical effectiveness is mainly associated with increased micro-scale roughness, which improves fibrin retention, mechanical interlocking, and early bone formation around the implant surface^{12,14,34}.

However, conventional SLA surfaces primarily modify the implant at the microstructural level and may not fully utilize nano-scale biological interactions or surface chemistry-mediated cellular responses. These limitations contributed to the development of more advanced surface engineering strategies intended to improve early cellular activity and accelerate osseointegration.

Nanostructured Surfaces and Biomimetic Design

Nanostructured implant surfaces were developed to reproduce certain characteristics of the natural extracellular matrix and improve biological interaction at the implant interface^{15,20–22}. Experimental studies demonstrated that nano-modified surfaces may increase protein adsorption, improve osteoblast adhesion, and stimulate early osteogenic differentiation. Several investigations also suggested that nanoscale surface features may influence cellular signaling pathways involved in osteoblast proliferation and bone formation^{21,51}. Nevertheless, interpretation of these findings should be approached cautiously because fabrication methods, nanopattern geometry, and surface characterization protocols vary considerably between studies^{20,22,43}. This heterogeneity limits direct comparison and complicates clinical translation.

Surface Chemistry and UV Photofunctionalization

An important finding in the current literature is the role of surface chemistry in addition to surface topography. UV photofunctionalization does not substantially change implant morphology but instead alters surface energy and hydrophilicity by reducing hydrocarbon contamination on titanium surfaces^{23–30}.

Improved wettability has been associated with enhanced protein adsorption, fibrin stabilization, and osteoblast attachment during early healing^{24–26}. Several studies reported increased bone-to-implant contact and improved early implant stability following UV treatment, particularly in compromised bone conditions and short implant protocols^{26–30,41}.

However, some limitations remain. The biological effects of UV activation may decrease over time, and standardized clinical protocols for routine application are still lacking^{29,30}.

Laser Surface Modification

Laser-based surface modification allows controlled alteration of implant micro- and nano-topography without introducing chemical contaminants^{31–33}. Experimental evidence suggests that laser-treated surfaces may improve osteoblast response, increase mechanical interlocking, and reduce bacterial adhesion^{31–33,50–52}.

Recent developments in picosecond and nanosecond laser technologies enabled the production of hybrid micro–nano surface structures associated with improved cellular activity and bone healing in

preclinical studies^{50,51}. Despite these promising results, most currently available evidence remains experimental, and long-term clinical studies are still limited.

Hydrophilicity and Early Biological Response

The reviewed literature indicates that surface hydrophilicity is an important factor during early implant healing. Increased wettability may improve blood interaction with the implant surface, promote fibrin network formation, and facilitate migration of osteogenic cells^{24–26,34,35}.

UV photofunctionalization represents one approach for restoring hydrophilicity of aged titanium surfaces and improving early biological response^{23–30}. These findings support the concept that both surface chemistry and topography contribute to successful osseointegration.

Osseointegration and Antimicrobial Considerations

One important issue identified in the current literature is the relationship between implant surface roughness and bacterial adhesion. Although roughened surfaces generally improve osteoblastic activity and osseointegration, they may also increase plaque accumulation and peri-implant bacterial colonization^{4,28,33,45–47}.

Nanostructured and laser-modified surfaces demonstrated favorable antimicrobial potential in several experimental studies while maintaining osteogenic properties^{31,33,47,52,53}. However, additional clinical evidence is required to determine the long-term effectiveness of these strategies in peri-implant disease prevention.

Additive Coatings and Long-Term Stability

Additive coatings such as hydroxyapatite and calcium phosphate may improve early bone apposition and osteoconductivity^{18,19}. Nevertheless, concerns remain regarding coating durability, delamination, and mechanical stability under long-term functional loading conditions. For this reason, recent research has increasingly focused on thinner bioactive coatings and surface functionalization strategies that preserve implant mechanical integrity while improving biological response.

Clinical Implications for Short Implants

The findings of this review are clinically relevant for short implants and compromised bone conditions. Surface modification may partially compensate for reduced implant length by improving early bone response and implant stability^{41–43}.

UV-treated, hydrophilic, and nano-modified surfaces demonstrated favorable outcomes in several short implant studies, including improved early stability and high survival rates^{27–30,41,42}. These approaches may help reduce the need for extensive bone augmentation procedures in selected clinical situations.

Limitations of Current Evidence

Interpretation of the current evidence is limited by several methodological factors, including:

- heterogeneity in study design and implant systems,
- variability in surface characterization methods,
- inconsistent outcome assessment protocols,
- predominance of in vitro and animal studies for newer technologies,
- and limited long-term randomized clinical trials.

These limitations reduce the strength of direct comparisons between implant surface technologies.

Future Perspectives

Future investigations should focus on:

- standardized implant surface characterization methods,
- long-term randomized controlled clinical trials,
- direct comparative studies between emerging technologies,
- and development of multifunctional implant surfaces combining osteogenic and antimicrobial properties.

Current trends suggest that future implant surface designs may combine micro-scale roughness, nano-scale surface architecture, and physicochemical bioactivation to improve both biological response and clinical performance^{34,35,50,52}.

CONCLUSION

This review demonstrates that implant surface modification plays a pivotal role in enhancing osseointegration and clinical success. While SLA surfaces remain the benchmark for reliability, emerging technologies—particularly nanostructuring, UV photofunctionalization, and laser modification—offer significant potential to further improve biological outcomes. However, the translation of these innovations into routine clinical practice requires

high-quality long-term evidence and standardized protocols. The future of implantology lies in the development of bioactive, multifunctional surfaces capable of simultaneously promoting bone regeneration and preventing microbial complications.

DECLARATIONS

Ethical Approval

Not applicable.

Competing Interests

The authors declare no conflict of interest.

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REVIEW ARTICLE

FUSOBACTERIUM NUCLEATUM AND COLORECTAL CANCER: FROM ORAL DYSBIOSIS TO TUMOUR PROGRESSION. A NARRATIVE REVIEWHelen Bollen¹, Bodine Reitsma¹, Curd Bollen²¹DH, University Centre Leuven-Limburg, Department Oral Hygiene, Belgium² DDS, PhD, MSc, PGCert (Multiple Institutions), Professor Department of Surgical Stomatology and Maxillo-Facial Surgery, Yerevan State Medical University, Belgium**Corresponding author:** Curd Bollen, Professor Department of Surgical Stomatology and Maxillo-Facial Surgery, Yerevan State Medical University, Belgium, E-mail curdbollen@me.com**Received:** Apr 14, 2026; **Accepted:** May 20, 2026; **Published:** May 27, 2026**ABSTRACT**

The relationship between oral health and systemic disease has become an important field of research in recent years. Among oral microorganisms, *Fusobacterium nucleatum* (*F. nucleatum*) has attracted considerable attention because of its frequent detection in colorectal cancer (CRC) tissue and its potential role in tumour progression. *F. nucleatum* is a Gram-negative anaerobic bacterium commonly associated with periodontal disease and oral dysbiosis. Increasing evidence suggests that this microorganism may contribute to colorectal carcinogenesis through inflammatory signalling, immune modulation, epithelial barrier disruption, and chemoresistance.

This narrative review summarizes the current evidence regarding the biological mechanisms linking *F. nucleatum* to CRC. Attention is given to bacterial adhesins such as FadA and Fap2, activation of the TLR4/MyD88/NF-κB pathway, immune escape mechanisms involving TIGIT and PD-L1, and the role of *F. nucleatum* in chemotherapeutic resistance. Clinical studies consistently demonstrate increased intratumoral abundance of *F. nucleatum* in advanced CRC stages and associations with poorer prognosis and reduced survival.

Although causality has not yet been definitively established, the available mechanistic and clinical evidence strongly supports the concept that *F. nucleatum* functions as a disease-modifying organism within the colorectal tumour microenvironment. Furthermore, these findings highlight the potential importance of periodontal health and interdisciplinary collaboration between dental and medical professionals.

Keywords: *F. nucleatum*; colorectal cancer; oral microbiome; periodontitis; tumour microenvironment; immune modulation; chemoresistance

INTRODUCTION

The association between oral health and systemic disease has gained increasing scientific attention over the past decade ^{1,2,3,4}. Oral microorganisms are no longer considered exclusively local pathogens, as mounting evidence demonstrates their ability to influence distant organs and systemic inflammatory processes. Periodontal disease has been associated with several systemic disorders, including cardiovascular disease, diabetes mellitus, neurodegenerative disorders, and malignancies.

Among oral pathogens, *F. nucleatum* has emerged as one of the most extensively investigated bacteria in

relation to colorectal cancer (CRC) ^{5,6,7,8}. CRC remains one of the most common malignancies worldwide and represents a major cause of cancer-related mortality ². The disease develops through a complex interaction between genetic susceptibility, environmental factors, chronic inflammation, and alterations in the intestinal microbiome. *F. nucleatum* is a Gram-negative obligate anaerobic bacterium that normally resides within the oral cavity and plays an important role in periodontal biofilm maturation ^{9,10}. However, increasing evidence indicates that this bacterium may translocate from the oral cavity to the gastrointestinal tract and preferentially colonize colorectal tumour tissue. Multiple studies have demonstrated significantly increased levels of *F. nucleatum* within CRC tissue compared with healthy

The objective of this narrative review is to summarize current knowledge regarding the relationship between *F. nucleatum* and colorectal cancer, with particular focus on molecular mechanisms, tumour progression, immune modulation, and potential implications for oral healthcare professionals.

Biology of *F. nucleatum*

F. nucleatum is a spindle-shaped Gram-negative anaerobic bacterium that forms part of the normal oral microbiota. Under physiological conditions, it behaves as a commensal organism; however, in dysbiosis conditions such as gingivitis and periodontitis, it may act as an opportunistic pathogen. The bacterium possesses several virulence factors that contribute to adhesion, invasion, and biofilm formation. One of the most important characteristics of *F. nucleatum* is its ability to function as a “bridge organism” within polymicrobial biofilms, connecting early and late colonizers during biofilm maturation (Fig. 1).

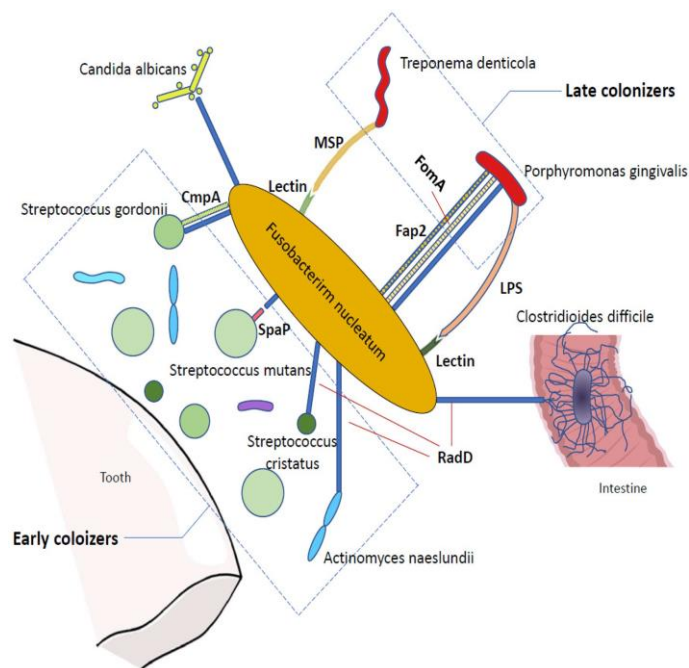


Figure 1. Schematic representation of the role of *F. nucleatum* in oral and intestinal microbial interactions and the adhesins and mechanisms involved that contribute to colonization and association with other microorganisms.

Several outer membrane proteins contribute to its pathogenicity^{10,14,15}:

- **RadD:** mediates interspecies bacterial coaggregation and biofilm architecture;

- **FadA:** enables adhesion and invasion of epithelial cells;
- **Fap2:** interacts with host glycans and immune receptors.

These virulence factors allow *F. nucleatum* to establish close interactions with both host tissues and neighbouring microorganisms^{14,16,17}.

Within periodontal tissues, *F. nucleatum* contributes to chronic inflammation through activation of epithelial and immune cells, inducing production of pro-inflammatory cytokines such as IL-6, IL-8, and TNF- α .

Potential Routes from the Oral Cavity to the Colon

Several mechanisms have been proposed to explain how oral *F. nucleatum* reaches colorectal tissue.

Hematogenous dissemination

Experimental studies suggest that hematogenous spread may represent the most plausible route⁹. Periodontal inflammation compromises the integrity of gingival tissues and blood vessels, potentially allowing oral bacteria to enter the bloodstream. Animal studies demonstrated that intravenous inoculation of *F. nucleatum* resulted in significantly more efficient colonization of colorectal tumours than oral administration. Moreover, genomic analyses have shown similarities between oral and colorectal strains of *F. nucleatum*, supporting the hypothesis of oral-to-intestinal bacterial dissemination^{13,18}.

Gastrointestinal route

Daily swallowing of saliva containing oral bacteria may also contribute to gastrointestinal exposure. However, gastric acidity and competition with resident intestinal microbiota substantially limit bacterial survival. Consequently, the oral-intestinal route appears less efficient than hematogenous dissemination.

Nevertheless, dysbiosis, antibiotic exposure, chronic inflammation, or altered intestinal permeability may create favourable conditions for intestinal colonization.

Molecular Mechanisms Linking *F. nucleatum* to CRC

Adhesion and epithelial invasion

One of the most extensively studied virulence factors is FadA, an adhesin capable of binding to E-cadherin on epithelial cells^{5,35}. This interaction disrupts epithelial integrity and activates the Wnt/ β -catenin signalling

pathway. Activation of Wnt/ β -catenin signalling stimulates expression of oncogenes such as *MYC* and *CCND1*, promoting cellular proliferation and tumour progression^{19,20}. Additionally, Fap2 binds specifically to the Gal-GalNAc glycan motif, which is highly expressed on colorectal tumour cells²¹. This selective interaction may explain the preferential accumulation of *F. nucleatum* within colorectal tumours.

Inflammatory signalling

Following epithelial invasion, bacterial components such as lipopolysaccharides activate Toll-like receptor 4 (TLR4) on immune cells^{22,23,24}. Subsequent activation of the MyD88/NF- κ B signalling cascade results in production of pro-inflammatory cytokines including IL-6, IL-8, and TNF- α .

This chronic inflammatory microenvironment contributes to multiple tumour-promoting processes^{24,25,26}.

- enhanced cellular proliferation;
- angiogenesis;
- genomic instability;
- inhibition of apoptosis;
- tumour progression.

The persistent inflammatory state generated by *F. nucleatum* may therefore facilitate carcinogenesis and accelerate tumour development.

Immune Modulation and Tumour Escape

An important aspect of *F. nucleatum*-associated tumour biology involves immune evasion.

The bacterial adhesin Fap2 binds to the TIGIT receptor present on T lymphocytes and natural killer (NK) cells²⁷. This interaction suppresses antitumor immune activity and reduces cytotoxic responses against malignant cells. Furthermore, *F. nucleatum* has been associated with increased expression of PD-L1 within the tumour microenvironment, contributing to immune suppression.

Additional mechanisms include recruitment of:

- myeloid-derived suppressor cells (MDSCs);
 - tumour-associated macrophages (TAMs).
- Figure 2: Overview of TNM classification in CRC. T indicates the size of the primary tumour, N the number of involved regional lymph nodes and M the presence of metastases

Together, these mechanisms create an immunosuppressive microenvironment that favours tumour survival and progression^{25,26,28}.

F. nucleatum and Chemoresistance

Several studies suggest that *F. nucleatum* contributes to reduced sensitivity to chemotherapy^{15,16}.

Particularly relevant is its association with resistance to:

- 5-fluorouracil;
- oxaliplatin.

Mechanistically, *F. nucleatum* appears to stimulate autophagy through activation of the TLR4/MyD88 pathway. Reduced expression of specific microRNAs, including miR-18a and miR-4802, has been implicated in this process. Additionally, recent studies indicate that *F. nucleatum* inhibits ferroptosis through activation of the E-cadherin/ β -catenin/GPX4 axis, thereby increasing tumour cell survival under oxidative stress conditions²⁹.

Other investigations suggest that *F. nucleatum* may enhance stem-cell-like properties within tumour cells, further contributing to recurrence and treatment resistance.

Clinical Implications and Prognostic Value

Clinical studies consistently demonstrate increased intratumoral abundance of *F. nucleatum* in advanced CRC stages^{5,30,31}.

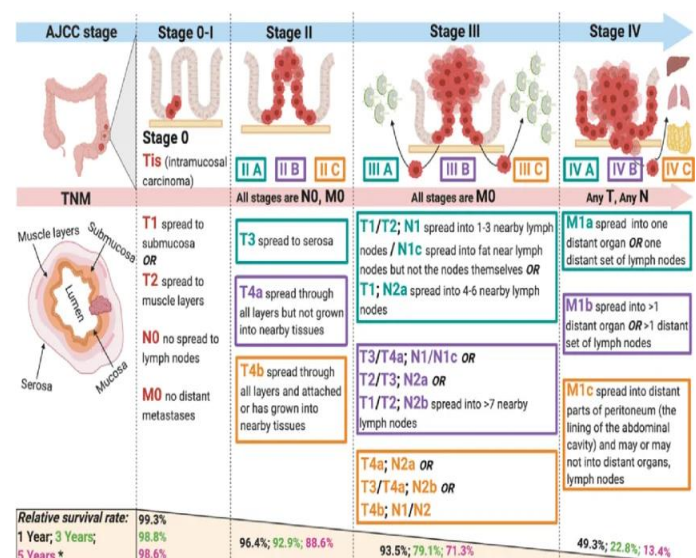


Figure 2. Overview of TNM classification in CRC. T indicates the size of the primary tumour, N the number of involved regional lymph nodes and M the presence of metastases.

Higher bacterial levels have been associated with (Fig. 2):

- advanced TNM stage;
- poorer tumour differentiation;
- microsatellite instability (MSI);
- increased recurrence risk;
- reduced overall survival.

Meta-analyses further support the association between elevated *F. nucleatum* levels and unfavourable prognosis^{11,12,30,31}.

Despite these findings, current evidence remains predominantly observational. Therefore, definitive causal conclusions cannot yet be established.

Nevertheless, the available mechanistic and clinical evidence strongly suggests that *F. nucleatum* acts as a disease-modifying organism that contributes to tumour progression and immune dysregulation.

Relevance for Periodontal and Oral Healthcare Professionals

Current evidence does not support the use of oral *F. nucleatum* detection as a screening tool for colorectal cancer³. The bacterium is frequently present in healthy individuals and lacks sufficient specificity for diagnostic purposes.

However, periodontal inflammation is associated with increased abundance of *F. nucleatum* and other pathogenic oral microorganisms. Consequently, maintenance of periodontal health may contribute to reducing systemic inflammatory burden.

Oral healthcare professionals therefore play an important role in:

- prevention and treatment of periodontal disease;
- reduction of oral dysbiosis;
- patient education regarding oral-systemic health;
- interdisciplinary collaboration with medical professionals.

Particularly in oncological patients, optimal oral health may improve quality of life and reduce complications associated with systemic inflammation.

Future Perspectives

Future research should focus on longitudinal and interventional studies capable of clarifying the causal relationship between *F. nucleatum* and colorectal

carcinogenesis^{3,6}.

Potential future directions include innovative microbiome-targeted strategies and precision-oncology approaches^{4,32,33,34}:

- microbiome-targeted therapies;
- modulation of oral dysbiosis;
- bacteriophage therapy;
- probiotic interventions;
- targeted inhibition of bacterial virulence factors.

Additionally, a deeper understanding of tumour-microbiome interactions may facilitate development of personalized therapeutic strategies.

CONCLUSION

Increasing evidence supports a significant association between *Fusobacterium nucleatum* and colorectal cancer progression. Through mechanisms involving epithelial invasion, inflammatory signalling, immune modulation, and chemoresistance, *F. nucleatum* appears capable of promoting a tumour-supportive microenvironment.

Although definitive causality has not yet been established, current mechanistic and clinical evidence strongly suggests that *F. nucleatum* functions as a disease-modifying organism within colorectal carcinogenesis.

These findings further emphasize the importance of oral health and interdisciplinary collaboration between dental and medical professionals. Periodontal management and reduction of oral dysbiosis may represent clinically relevant components of integrated patient care.

DECLARATIONS

Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

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CASE REPORT

NON-SURGICAL ENDODONTIC TREATMENT OF CHRONIC APICAL PERIODONTITIS WITH EXTENSIVE PERIAPICAL AND FURCATION BONE DESTRUCTION: A CASE REPORT WITH 18-MONTH FOLLOW-UP

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ABSTRACT

Background: Chronic apical periodontitis associated with extensive periapical bone destruction (>10 mm) and furcation involvement represents a significant endodontic challenge and is often considered prognostically unfavorable.

Objective: To describe the non-surgical endodontic management of chronic apical periodontitis associated with an extensive periapical lesion and furcation involvement, with emphasis on long-term clinical and radiographic outcomes.

Case Presentation: A 26-year-old male patient presented with acute purulent periostitis associated with tooth 4.7. Clinical and CBCT examination revealed extensive periapical bone destruction involving the furcation region. Initial management included surgical drainage and antibiotic therapy (amoxicillin/clavulanic acid 1000 mg twice daily for 5 days). Following resolution of acute symptoms, stepwise endodontic treatment was performed using chemomechanical preparation with sodium hypochlorite and EDTA, intracanal calcium hydroxide medication for 21 days, and final obturation by vertical condensation of heated gutta-percha with AH Plus sealer. Clinical and radiographic follow-up evaluations were performed at 3, 6, 12, and 18 months.

Results: Acute inflammatory symptoms resolved completely within 5 days. Progressive radiographic bone regeneration was observed during follow-up. At 18 months, CBCT imaging demonstrated complete radiographic healing of the periapical and furcation defects with restoration of normal bone architecture. Clinically, the tooth remained asymptomatic and fully functional, with normal percussion response and physiologic mobility.

Conclusions: This case demonstrates that extensive periapical lesions with furcation involvement of primary endodontic origin may be successfully managed using a non-surgical approach. Thorough chemomechanical disinfection, intracanal calcium hydroxide medication, adequate coronal sealing, and systematic follow-up contributed to favorable long-term healing without surgical intervention.

Keywords: chronic apical periodontitis; periapical bone regeneration; furcation involvement; calcium hydroxide; vertical condensation; non-surgical endodontic treatment

INTRODUCTION

Chronic apical periodontitis (CAP) represents one of the most prevalent sequelae of pulp necrosis and bacterial infection of the root canal system, characterized by inflammatory and destructive changes in periapical tissues^{1,2}. Histopathological studies have demonstrated that periapical lesions are primarily maintained by persistent intraradicular infection rather than true cystic transformation in most cases^{3,4}. The

extent of periapical bone destruction varies considerably; however, lesions exceeding 10 mm in diameter are generally considered extensive and are associated with a more complex healing pattern, often requiring prolonged follow-up and careful therapeutic planning⁵. When such destruction involves the furcation area of multirooted teeth, diagnostic complexity increases substantially, as accurate differentiation between primary endodontic lesions, primary

periodontal lesions, and combined endodontic-periodontal involvement is essential for appropriate treatment planning and prognosis^{4,5}.

Cone-beam computed tomography (CBCT) has significantly improved diagnostic accuracy in such cases by enabling three-dimensional assessment of lesion extent and furcation involvement⁸. Traditionally, teeth presenting with extensive periapical bone loss and furcation involvement have been considered to have a guarded or unfavorable prognosis, often leading to surgical intervention (apicoectomy, hemisection, root resection) or extraction^{6,7,9,10}. However, contemporary endodontic literature increasingly demonstrates that nonsurgical root canal treatment, when performed with meticulous chemomechanical disinfection and appropriate intracanal medication, can achieve high rates of healing and even complete radiographic bone regeneration in cases with large periapical lesions⁸⁻¹³. Long-term clinical studies further support that adequate disinfection and obturation protocols may result in successful healing of extensive periapical radiolucencies without surgical intervention^{11,12}. The biological basis of periapical healing has been extensively described, indicating that resolution of inflammation and bone regeneration occur following elimination of intracanal infection and adequate sealing of the root canal system^{3,13}. Successful nonsurgical endodontic outcomes in cases of primary endodontic pathology with extensive bone loss depend on multiple interrelated factors, including accurate diagnosis, absence of prior endodontic intervention, effective chemomechanical debridement, high-quality irrigation with sodium hypochlorite and EDTA, use of intracanal medicaments—particularly calcium hydroxide due to its antimicrobial and tissue-healing properties¹⁴—and achievement of three-dimensional hermetic obturation with reliable coronal sealing^{2,10,11,12,15}. Collectively, these factors contribute to the elimination of intracanal infection and preservation of the periapical healing potential necessary for predictable bone regeneration. The present case report describes the successful non-surgical endodontic management of a mandibular second molar (4.7) presenting with extensive periapical destruction (>10 mm) extending into the furcation region following acute purulent periostitis. The case highlights the importance of accurate diagnosis, effective infection control, and structured follow-up in achieving favorable long-term healing without surgical intervention.

CLINICAL CASE REPORT

A 26-year-old male patient presented to the clinic in May 2024 in an emergency condition, complaining of

intense, radiating pain in the right mandibular region, exacerbated by occlusal contact and tooth palpation. The symptoms were accompanied by headache, general malaise, and marked sensitivity in the region of tooth 4.7. The medical history revealed intermittent dental discomfort over several years; however, following spontaneous resolution of symptoms, the patient did not seek dental care.

Objective Clinical Findings

Tooth 4.7 (mandibular right second molar) presented with a preserved natural-colored crown, compatible with adjacent teeth, and an existing occlusal restoration with apparently intact marginal adaptation. Percussion along both longitudinal and horizontal axes elicited severe pain. Palpation in the projection of the root apices and the vestibular fold was painful, and Grade I mobility of the tooth was observed. Localized swelling and mucosal erythema were present in the vestibular fold in the region of tooth 4.7. Adjacent teeth (4.6 and 4.8) responded positively to vitality testing using cold stimulation. The patient's general condition was satisfactory, with a body temperature of 37.6°C and stable vital signs.

Radiological Assessment

Periapical radiography and cone-beam computed tomography (CBCT) revealed an extensive area of bone destruction in the periapical region, exceeding 10 mm in diameter with indistinct borders. The lesion extended to the interradiacal septum (furcation area), demonstrating pronounced bone rarefaction involving the apical third of all roots.

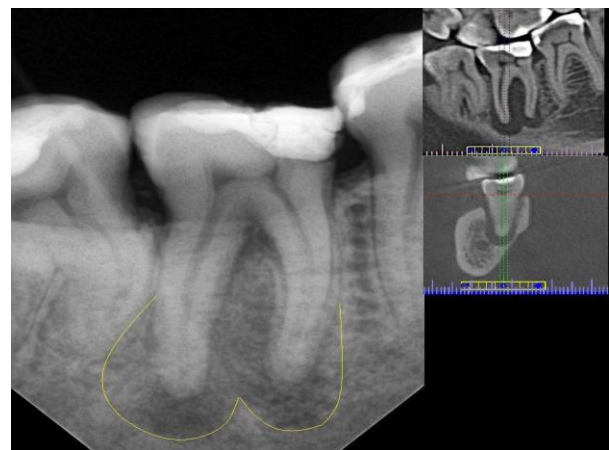


Figure 1. Preoperative CBCT and periapical radiograph demonstrating an extensive area of bone destruction in the periapical region, exceeding 10 mm in diameter with indistinct borders. The lesion extends to the interradiacal septum (furcation area), showing pronounced bone rarefaction involving the apical third of all roots.

Diagnosis

Acute purulent periostitis in the active phase, secondary to chronic apical periodontitis of tooth 4.7 with extensive furcation involvement.

Treatment Protocol

Stage 1. Emergency Management

Under topical and infiltration anesthesia (articaine 4% with epinephrine 1:200,000, 1.8 mL), a linear incision was made along the vestibular fold in the region of tooth 4.7, approximately 1.5 cm in length. Purulent exudate was evacuated, and a rubber drain was placed for 48 hours. Empirical antimicrobial therapy was initiated with amoxicillin/clavulanic acid (Amoxiclav) 1000 mg twice daily for 5 days, supplemented with probiotic therapy (Bifitsin, 1 capsule daily for 8 days). Oral rinses with 0.05% chlorhexidine solution were prescribed three to four times daily. Within 5 days, acute inflammatory symptoms completely resolved, with reduction of pain and swelling, normalization of body temperature, decreased tooth mobility, and marked reduction in percussion sensitivity. No complications were observed.

Stage 2. Endodontic Treatment

Seven days after initial presentation, endodontic treatment was initiated under rubber dam isolation. Endodontic access was established through the occlusal surface following removal of the existing restoration. Working length determination was performed using both radiographic methods and an electronic apex locator. Mechanical preparation of the root canals was carried out using rotary NiTi instruments (SOCO system), with ISO sizes 30 for the mesiobuccal and mesiolingual canals and ISO size 40 for the distal canal, using a 0.06 taper protocol.

Chemical irrigation protocol included 5% sodium hypochlorite activated with an EndoActivator system, followed by 17% EDTA for 60 seconds, and a final rinse with sterile distilled water. The canals were temporarily dressed with a calcium hydroxide-based paste (Calasept) delivered via a canal carrier and sealed with a temporary restoration for 21 days.

Stage 3. Final Obturation

After 3 weeks, the canals were re-irrigated, dried with sterile paper points, and obturated using vertical condensation of thermoplasticized gutta-percha with AH Plus sealer. The coronal portion was restored with a

light-cured composite resin, ensuring an adequate coronal seal.



Figure 2. Immediate postoperative periapical radiograph demonstrating completion of root canal obturation using vertical condensation of thermoplasticized gutta-percha with AH Plus sealer. The image shows adequate and homogeneous filling of all three canal systems, with proper apical sealing and absence of voids.

Clinical Follow-up Assessment

Clinically, the patient was followed up at 3, 6, 12, and 18 months after treatment. At all follow-up visits, the patient remained completely asymptomatic, reporting no pain or functional discomfort. Periodontal examination revealed probing depths within 2–3 mm throughout the follow-up period, with no persistent periodontal defects or furcation involvement. Tooth mobility, initially recorded as Grade I preoperatively, returned to physiological levels and remained stable throughout all subsequent evaluations. Percussion testing consistently revealed no tenderness.

Radiological Progression

Radiographically, progressive healing was observed over the follow-up period. At 6 and 12 months, partial bone regeneration was evident in both the periapical region and the furcation area, indicating ongoing reparative activity. Progressive reduction of the radiolucent area with re-establishment of trabecular bone pattern was noted during this period. Compared to the initial extensive periapical radiolucency (>10 mm), marked structural improvement was evident.

At the 18-month follow-up, CBCT imaging demonstrated complete radiographic healing of the lesion. The previously observed periapical radiolucency was fully resolved, with re-establishment of the lamina

dura along the entire root length. The interradicular septum exhibited normal trabecular density without evidence of residual rarefaction, confirming complete restoration of bone architecture in both periapical and furcation regions (Figure 3). The patient reported full functional recovery and high satisfaction with the outcome.



Figure 3. CBCT follow-up at 18 months post-treatment demonstrating complete restoration of periapical and furcation bone architecture. The previous radiolucent lesion has undergone complete radiographic healing. The lamina dura is clearly re-established along the entire root length, and the interradicular septum shows normal trabecular density without signs of rarefaction, indicating full recovery of bone structure in both periapical and furcation regions.

DISCUSSION

The favorable prognosis achieved in this case was substantially facilitated by the patient's young age (26 years) and the absence of previous endodontic intervention—factors consistently identified in the literature as significant positive prognostic indicators for nonsurgical root canal treatment outcomes ^{2,10}. Young age is associated with superior regenerative capacity of periapical tissues and enhanced vascular response, which likely contributed to the observed progression from partial healing at 6–12 months to complete radiographic resolution at 18 months.

The acute presentation with purulent periostitis, traditionally considered a prognostically unfavorable complication, was effectively managed through prompt surgical drainage and short-term antimicrobial therapy (amoxicillin/clavulanic acid 1000 mg twice daily for 5 days). Complete resolution of acute inflammatory signs within 5 days is consistent with evidence indicating that timely elimination of the infectious focus significantly improves subsequent endodontic healing outcomes ^{3,15}.

This highlights the importance of controlling acute odontogenic infection prior to definitive endodontic intervention.

The endodontic protocol incorporated contemporary evidence-based disinfection strategies, including sodium hypochlorite activation using EndoActivator, prolonged intracanal calcium hydroxide medication for 21 days, and three-dimensional obturation using vertical condensation of thermoplasticized gutta-percha with AH Plus sealer. These measures are supported by literature demonstrating that enhanced irrigation, intracanal medicaments, and adequate obturation significantly improve healing of large periapical lesions by maximizing microbial elimination and promoting periapical repair ^{11,14,15}.

Vitality testing of adjacent teeth (4.6 and 4.8), together with the absence of prior endodontic treatment in tooth 4.7, confirmed the primary endodontic origin of the lesion, effectively excluding a primary periodontal etiology. This distinction is critical in cases involving furcation regions, where endodontic-periodontal lesions may present similar radiographic features ^{4,5}.

The observed healing pattern—partial radiographic regeneration at 6–12 months followed by complete resolution at 18 months—is consistent with previously reported outcomes of nonsurgical endodontic treatment in teeth with extensive periapical lesions, particularly when calcium hydroxide is used as an intracanal medicament ^{9,12}. CBCT-based follow-up findings in this case align with literature demonstrating the superiority of three-dimensional imaging in accurately monitoring periapical healing and furcation bone regeneration ^{16,17}.

Complete re-establishment of lamina dura and trabecular bone architecture without the use of regenerative surgical techniques or biomaterials further supports the concept that orthograde endodontic treatment remains the primary treatment modality in cases of primary endodontic pathology with extensive bone destruction. This is in agreement with long-term clinical data demonstrating high survival and healing rates of nonsurgically treated teeth when adequate disinfection and obturation protocols are followed ^{8,11}.

This case emphasizes the importance of individualized, evidence-based treatment planning, including timely management of acute infection, accurate diagnosis, effective chemomechanical disinfection, and strict coronal sealing. Collectively, these factors are essential for achieving predictable tooth preservation and radiographically confirmed bone regeneration even in cases with extensive furcation involvement.

LIMITATIONS

This report has inherent limitations typical of single case reports, including limited generalizability. The outcome represents a favorable clinical scenario influenced by positive prognostic factors such as young age, primary endodontic pathology, and good patient compliance. Histological confirmation of bone regeneration was not performed. Long-term stability beyond 18 months remains to be established, and variations in systemic conditions or anatomical complexity may influence outcomes in other cases.

CONCLUSION

This clinical case demonstrates successful nonsurgical endodontic treatment of a mandibular second molar (4.7) in a 26-year-old patient presenting with extensive periapical bone destruction (>10 mm) extending into the furcation region, associated with acute purulent periostitis. Complete radiographic healing of both periapical and furcation bone defects was achieved at 18 months, demonstrating the regenerative potential of periapical tissues when managed through timely infection control, effective antimicrobial strategies, meticulous chemomechanical disinfection, intracanal calcium hydroxide medication, three-dimensional obturation, and adequate coronal sealing.

The absence of complications, preservation of tooth function, and elimination of the need for surgical intervention or regenerative biomaterials support the concept that orthograde endodontic treatment remains the preferred approach in primary endodontic lesions with extensive bone destruction. These findings are consistent with contemporary evidence demonstrating favorable long-term outcomes of nonsurgical root canal therapy when strict treatment protocols are followed.

This case highlights the therapeutic potential of conservative endodontic management in young patients with preserved coronal structure, even in the presence of extensive radiographic periapical and furcation involvement.

DECLARATION

Ethics Approval and Consent to Participate

This case was conducted in accordance with the principles of the Declaration of Helsinki. The patient provided written informed consent for diagnostic procedures, treatment interventions, and publication of clinical data and radiological images in anonymized form. The investigation was approved by the appropriate institutional ethics committee.

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Competing Interests

The authors declare that they have no competing interests related to this publication.

Author Contributions

The following describes the individual contributions of each author to this manuscript:

Magomedov Ibragim Nabiylulaevich analyzed radiological findings and contributed to treatment planning.

Supiev Lugman Pastaminovich conducted the clinical examination, performed endodontic treatment, and prepared the primary draft of the manuscript.

Omarov Muslim Omarovich Critical analysis of content, clinical perspective, and manuscript review.

Gadzhiev Muradkhan Gadzhigishievich Manuscript preparation and formatting.

Merdanova Leyla Merdanovna reviewed the literature and assisted in preparation of the clinical narrative.

Ibragimova Sagdijat Arsenovna Literature review, data analysis, and contribution to manuscript writing.

Ordashev Khasan Alievich supervised the clinical case, provided expert consultation, and edited the final manuscript.

All authors reviewed and approved the final version of the manuscript.

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CLINICAL CASE SERIES

CLINICAL AND RADIOGRAPHIC OUTCOMES OF INTENTIONAL REIMPLANTATION OF IMPACTED MAXILLARY CANINES: A RETROSPECTIVE CASE SERIES WITH FIVE-YEAR FOLLOW-UP

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ABSTRACT

Background: Management of impacted maxillary canines remains a significant challenge in oral surgery and orthodontics. Although surgical exposure followed by orthodontic traction is considered the standard treatment, certain cases present with severe displacement, unfavorable angulation, or suspected ankylosis, making orthodontic repositioning difficult or unpredictable. In such situations, intentional reimplantation may offer a biologically based alternative for preserving the natural tooth.

Objective: To evaluate the clinical and radiographic outcomes of intentional reimplantation of impacted maxillary canines using standardized surgical and endodontic protocols.

Materials and Methods: This retrospective case series included 24 patients treated between 2021 and 2025 for impacted maxillary canines with an unfavorable prognosis for orthodontic traction. All patients underwent atraumatic surgical extraction, extraoral endodontic treatment when indicated, immediate reimplantation, and semi-rigid splint stabilization. Clinical and radiographic follow-up assessments were performed from the immediate postoperative period to a maximum of 5 years. Outcome measures included tooth retention, mobility, periodontal health, root resorption, ankylosis, and functional integration.

Results: All reimplanted canines remained functional throughout the available follow-up period, resulting in a 100% tooth retention rate. Clinical success, defined as functional stability without progressive root resorption, ankylosis, periodontal deterioration, or loss of function, was achieved in 22 of 24 cases (91.7%). Mild non-progressive external root resorption was observed in one patient (4.2%), while two patients (8.3%) demonstrated persistent Grade I mobility without functional impairment. No cases of infection, ankylosis, severe mobility, progressive root resorption, or tooth loss were identified. Radiographic evaluation demonstrated preservation of periodontal ligament space and stable alveolar bone support in the majority of cases.

Conclusion: Intentional reimplantation of impacted maxillary canines may represent a viable tooth-preserving treatment option in carefully selected cases where orthodontic repositioning is not feasible or is associated with poor prognosis. Preservation of periodontal ligament vitality, atraumatic surgical handling, minimization of extraoral time, and appropriate postoperative stabilization appear to be critical determinants of favorable outcomes. Further prospective multicenter studies with larger patient cohorts are required to validate long-term predictability and identify prognostic factors influencing treatment success.

Keywords: Impacted canine; reimplantation; periodontal ligament; tooth transplantation; root resorption

INTRODUCTION

Impaction of maxillary canines represents one of the most common disturbances of dental eruption after third molars, with a reported prevalence ranging from 1% to 3% in the general population.¹ The permanent

maxillary canine plays a critical role in facial esthetics, dental arch integrity, functional occlusion, and canine-guided disclusion. Failure of eruption may result in several clinical complications, including root resorption of adjacent teeth, cystic changes, periodontal damage,

malocclusion, and long-term esthetic and functional impairment.^{2,3} Consequently, early diagnosis and appropriate management of impacted canines are considered essential components of contemporary orthodontic and oral surgical practice⁴.

The etiology of maxillary canine impaction is multifactorial and involves a combination of genetic, systemic, and local anatomical factors (table1)⁵.

Table 1. Major Etiological Factors Associated with Impacted Maxillary Canines

Etiological Category	Representative Factors
Local	Space deficiency, retained deciduous canines, ankylosis, supernumerary teeth, odontogenic pathology, trauma, eruption disturbances, and adjacent tooth anomalies.
Systemic	Skeletal syndromes, endocrine disorders, metabolic abnormalities, vitamin deficiencies, and radiation exposure.
Genetic	Tooth germ displacement, developmental anomalies, hereditary factors, and craniofacial defects.

Proposed etiological mechanisms include arch length deficiency, ectopic positioning of the tooth germ, abnormal eruption pathway, prolonged retention or ankylosis of the primary canine, and hereditary influences affecting eruption guidance.^{6,7}

Because the severity and spatial position of impacted canines may vary considerably, accurate radiographic localization is fundamental for treatment planning and prognosis assessment. Panoramic radiography remains a routine diagnostic tool; however, cone-beam computed tomography (CBCT) has significantly improved three-dimensional evaluation of impacted teeth, adjacent root relationships, angulation, and alveolar bone morphology.^{8,9}

Several radiographic classification systems have been proposed to evaluate the position and treatment prognosis of impacted maxillary canines. Among these, the Ericson and Kurol classification is widely used to assess mesiodistal position, angulation, and proximity to adjacent teeth using panoramic radiographs.^{10,11} Increased mesial displacement and severe angulation have been associated with greater treatment complexity, prolonged orthodontic treatment duration, and increased risk of adjacent root resorption.

CBCT-based evaluation has further enhanced the ability to determine the severity of impaction and potential feasibility of orthodontic repositioning.

Table 2. Ericson and Kurol Radiographic Classification of Impacted Maxillary Canines and Clinical Implications

Parameter	Classification	Clinical Significance
Sector 1	Distal to the lateral incisor axis	Favorable eruption prognosis
Sector 2	Overlapping distal half of lateral incisor root	Preventive extraction of primary canine often effective
Sector 3	Overlapping mesial half of lateral incisor root	Moderate impaction; close orthodontic monitoring required
Sector 4	Overlapping central incisor axis	Severe impaction; surgical-orthodontic intervention often indicated
Sector 5	Mesial to central incisor axis	Very severe impaction with increased treatment complexity
α -angle <20°	Mild inclination	Favorable prognosis
α -angle 20–30°	Moderate inclination	Interceptive treatment may be successful
α -angle >30°	Severe inclination	Early surgical exposure and orthodontic traction recommended

Various treatment modalities have been described for the management of impacted maxillary canines, including surgical exposure followed by orthodontic traction, extraction with prosthetic rehabilitation, autotransplantation, and intentional reimplantation.^{12,13} Orthodontic traction remains the gold standard treatment impacted maxillary canines because it preserves the natural tooth within the dental arch while maintaining periodontal support and functional integration.^{14,15}

Nevertheless, successful orthodontic repositioning depends on several factors, including favorable tooth position, sufficient arch space, adequate patient compliance, and absence of ankylosis. In cases involving severe displacement, unfavorable angulation, dilaceration, or suspected ankylosis, orthodontic traction may become unpredictable, excessively prolonged, or clinically contraindicated.^{16–18}

Intentional reimplantation is defined as the deliberate extraction of a tooth followed by reinsertion into its original or surgically prepared socket under controlled clinical conditions.^{19,20}

Historically, the procedure was considered a treatment of last resort because of concerns regarding ankylosis, root resorption, and long-term periodontal failure. However, advances in microsurgical techniques, modern endodontic protocols, biomaterials, and improved understanding of periodontal ligament biology have renewed clinical interest in intentional reimplantation as a conservative tooth-preserving

procedure.²¹

Intentional tooth replantation (ITR) is currently guided by two major clinical protocols. The first was published by the American Association of Endodontists (AAE) in 2019, and the second by the European Society of Endodontology (ESE) in 2021.²²

These guidelines provide comprehensive and detailed recommendations regarding case selection, clinical procedures, and postoperative follow-up. Both protocols aim to standardize clinical practice, improve procedural predictability, and enhance long-term tooth survival through evidence-based management strategies.

Despite increasing interest in this technique, standardized surgical protocols and evidence-based follow-up criteria for intentional reimplantation of impacted maxillary canines remain insufficiently established. The currently available literature consists predominantly of isolated case reports, case series, and studies extrapolated from autotransplantation and traumatic tooth avulsion research. Consequently, the predictability and long-term biological behavior of intentionally reimplanted impacted canines remain incompletely understood.²³⁻²⁵

The biological success of intentional reimplantation depends primarily on preservation of viable periodontal ligament (PDL) cells during extraction, handling, and reinsertion of the tooth. Viable PDL cells are essential for periodontal regeneration, cementum repair, and re-establishment of functional attachment between the root surface and alveolar bone. Damage to the periodontal ligament caused by mechanical trauma, dehydration, bacterial contamination, or prolonged extraoral time may compromise healing and increase the risk of inflammatory root resorption or ankylosis.²⁶⁻²⁸

For this reason, atraumatic extraction, maintenance of root surface hydration, and minimization of extraoral manipulation are considered critical determinants of successful healing.

Autotransplantation and intentional reimplantation share similar biological principles, particularly with respect to preservation of periodontal ligament vitality and promotion of periodontal healing. However, the two procedures differ in clinical indication and surgical approach. In autotransplantation, a donor tooth is transferred to a different recipient site, whereas intentional reimplantation involves reinsertion of the same tooth into its original or modified socket.^{28,29}

Both procedures require careful case selection,

atraumatic surgical handling, and appropriate stabilization to optimize periodontal healing and long-term survival.

Recent studies have reported survival rates ranging from approximately 70% to 90% for intentional reimplantation and tooth autotransplantation procedures when appropriate biological and surgical principles are respected, particularly with minimized extraoral time and preservation of periodontal ligament integrity.^{30,31} Nevertheless, evidence specifically evaluating intentional reimplantation of impacted maxillary canines remains limited, and most available reports involve small retrospective series with heterogeneous methodologies and variable follow-up durations.

Therefore, the aim of the present retrospective case series was to evaluate the clinical and radiographic outcomes of intentional reimplantation of impacted maxillary canines performed under standardized surgical and endodontic protocols and to assess the short-term biological stability, periodontal healing, and functional predictability of this treatment approach.

MATERIALS AND METHODS

2.1 Study Design

This retrospective case series was conducted to evaluate the clinical and radiographic outcomes of intentional reimplantation of impacted maxillary canines. A total of 24 consecutive patients treated between January 2021 and January 2025 were included. All surgical and endodontic procedures were performed according to standardized biological and operative protocols designed to preserve periodontal ligament vitality, minimize surgical trauma, and optimize periodontal healing.

Clinical records, operative reports, panoramic radiographs, cone-beam computed tomography (CBCT) scans, and follow-up examinations were retrospectively reviewed and analyzed.

2.2 Patient Selection

Twenty-four patients underwent intentional reimplantation of impacted maxillary canines during the study period. The cohort consisted of 13 males (54.2%) and 11 females (45.8%), with a mean age of 19.6 ± 4.2 years (range: 14–28 years) (Table3).

Table 3. Baseline Characteristics of the Study Population

Variable	Value
Number of patients	24
Mean age (years)	19.6 ± 4.2
Age range (years)	14–28
Male	13 (54.2%)
Female	11 (45.8%)
Tooth 13	12 (50.0%)
Tooth 23	12 (50.0%)
Palatal impaction	16 (66.7%)
Labial impaction	8 (33.3%)
Follow-up duration	Up to 5 years

All patients received comprehensive clinical and radiographic evaluation before treatment planning. Diagnostic assessment included intraoral examination, panoramic radiography, and CBCT imaging when indicated.

Radiographic analysis focused on canine position, angulation, relationship to adjacent teeth, root morphology, alveolar bone availability, and feasibility of orthodontic repositioning.

Intentional reimplantation was considered only when conventional orthodontic traction was associated with an unfavorable prognosis because of severe displacement, excessive angulation, ectopic eruption pathway, suspected ankylosis, root dilaceration, or anticipated prolonged orthodontic treatment.

Inclusion Criteria

Patients were included in the study when the following criteria were fulfilled:

- Presence of an impacted permanent maxillary canine
- Unfavorable prognosis for orthodontic traction or orthodontic repositioning
- Presence of a retained primary canine or an anatomically suitable recipient socket
- Adequate alveolar bone support for reimplantation
- Absence of systemic contraindications to oral surgical procedures
- Availability of postoperative follow-up records and radiographic evaluation

Exclusion Criteria

Patients were excluded from the study under the following conditions:

- Advanced periodontal disease involving adjacent teeth
- Poor oral hygiene or lack of compliance with postoperative care
- Active oral infection at the surgical site
- Severe systemic disease affecting wound healing or bone metabolism
- Immunocompromised status or uncontrolled systemic conditions
- Incomplete clinical or radiographic follow-up data

2.3 Clinical and Surgical Protocol

All procedures were performed under local anesthesia using a standardized surgical protocol designed to preserve periodontal ligament viability and optimize periodontal healing.

Preoperative Preparation

Before surgery, all patients underwent professional oral hygiene instructions and radiographic evaluation. CBCT imaging was used selectively to assess the exact three-dimensional position of the impacted canine, root angulation, relationship to adjacent teeth, and available recipient bone.

Surgical Extraction

A minimally traumatic surgical approach was used in all cases. Mucoperiosteal flap elevation and conservative osteotomy were performed when necessary to expose the impacted canine. The tooth was carefully luxated and extracted with minimal manipulation in order to reduce mechanical injury to the periodontal ligament and root surface.

Particular attention was given to preservation of cementum integrity and maintenance of viable periodontal ligament cells during extraction and handling.

Extraoral Endodontic Management

Following extraction, extraoral endodontic treatment was performed under sterile conditions in teeth with complete root formation when clinically indicated. Root canal instrumentation, irrigation, and obturation were completed using conventional endodontic techniques

and gutta-percha obturation. Throughout the extraoral phase, the root surface was continuously hydrated using sterile saline solution to prevent periodontal ligament desiccation. All efforts were made to minimize extraoral time, ideally maintaining the interval below 15–20 minutes whenever possible.

Recipient Site Preparation and Reimplantation

The recipient site was prepared conservatively using the socket of the retained primary canine or a surgically modified alveolar socket when necessary. Excessive curettage or compression of the socket walls was avoided to preserve vascular supply and facilitate periodontal ligament healing.

The treated canine was then repositioned into the recipient socket with careful axial alignment and passive adaptation. Excessive insertion force was avoided in order to minimize additional trauma to the root surface and surrounding alveolar bone.

Primary stability was assessed clinically immediately after reimplantation.

Splinting and Postoperative Management

Semi-rigid splinting was applied using composite resin and flexible orthodontic wire in all cases. Splints were maintained for approximately 2 to 4 weeks depending on initial stability and periodontal healing.

Postoperative management included systemic antibiotic therapy, nonsteroidal anti-inflammatory medication when indicated, and chlorhexidine mouth rinse twice daily for 7 to 14 days. Patients were instructed to maintain soft diet precautions and avoid excessive functional loading during the healing period.

2.4 Follow-Up Protocol

All patients underwent standardized postoperative clinical and radiographic follow-up evaluations. Clinical examinations were performed during the immediate postoperative period and subsequently at:

- 10 days
- 1 month
- 3 months
- 6 months
- 1 year
- Up to 3 years when long-term follow-up data were available

Follow-up assessment focused on periodontal healing,

tooth mobility, gingival condition, functional integration, and radiographic evidence of root or bone changes.

Periapical radiographs were obtained routinely during follow-up, while CBCT imaging was performed selectively in cases requiring additional evaluation of periodontal ligament space, root resorption, ankylosis, or alveolar bone condition.

2.5 Methodological Considerations

The present study was conducted under standardized surgical and follow-up conditions in order to improve consistency of treatment and outcome assessment. Nevertheless, clinical heterogeneity was present due to differences in patient age, canine position, angulation, depth of impaction, root morphology, and available recipient bone.

Because impacted maxillary canines demonstrate substantial anatomical variation, certain intraoperative modifications were occasionally necessary according to individual surgical requirements. Surgical timing, osteotomy extent, and recipient socket preparation were adapted depending on case complexity and anatomical conditions encountered during treatment.

Healing assessment was based on routine clinical examination and radiographic analysis. Parameters evaluated included tooth mobility, periodontal soft tissue adaptation, probing depth, alveolar bone stability, and radiographic signs of periodontal healing or pathological changes.

Follow-up duration varied among patients because of differences in treatment timing and availability of long-term recall examinations. Continuous monitoring was maintained whenever possible to evaluate periodontal stability and detect late complications such as external root resorption or ankylosis.

2.6 Outcome Measures and Evaluation Criteria

Clinical and radiographic outcomes were assessed using predefined evaluation criteria to improve reproducibility and objectivity of data interpretation.

Clinical Evaluation

Clinical assessment included evaluation of tooth mobility, periodontal condition, gingival health, pain, infection, and functional stability.

Tooth mobility was assessed according to a modified

Miller mobility classification system³¹:

- Grade 0: Physiological mobility (<0.2 mm)
- Grade I: Slight horizontal mobility (0.2–1 mm)
- Grade II: Moderate horizontal mobility (>1 mm)
- Grade III: Severe horizontal and vertical mobility

Periodontal evaluation included assessment of gingival adaptation, probing depth measurements when available, bleeding on probing, and presence of suppuration.

Periodontal health was defined as:

- probing depths ≤ 3 mm,
- absence of bleeding on probing,
- absence of suppuration,
- and clinically healthy peri-radicular soft tissue adaptation.

Functional success additionally required absence of persistent pain, masticatory discomfort, or occlusal instability.

Radiographic Evaluation

Radiographic evaluation was performed using periapical radiographs and CBCT imaging when clinically indicated.

The following radiographic parameters were assessed:

- Presence and continuity of the periodontal ligament space
- Integrity and continuity of the lamina dura
- Presence or absence of external root resorption
- Presence of ankylosis
- Alveolar bone stability and marginal bone levels
- Periapical radiolucency or inflammatory changes

External root resorption was categorized according to severity:

- Mild: superficial and non-progressive resorption
- Moderate: localized dentinal involvement
- Severe: progressive, circumferential, or extensive resorption

Radiographic ankylosis was defined as partial or complete loss of the visible periodontal ligament space

associated with direct continuity between root surface and surrounding alveolar bone.

Definition of Clinical Success

Clinical success was defined as:

- functional tooth retention,
- mobility Grade 0 or Grade I,
- absence of progressive external root resorption,
- absence of ankylosis,
- satisfactory periodontal condition,
- and maintenance of functional and esthetic integration throughout the follow-up period.

Cases demonstrating minor non-progressive complications without loss of function were classified as partial success rather than definitive treatment failure.

2.7 Case Report

Clinical Presentation

A patient presented with delayed eruption of a permanent maxillary canine associated with persistence of the corresponding primary canine. Clinical intraoral examination demonstrated absence of the permanent canine within the dental arch, accompanied by mild vestibular and palatal cortical prominence in the canine region. The retained primary canine exhibited reduced mobility and remained in functional occlusion.

Radiographic evaluation using panoramic imaging and cone-beam computed tomography (CBCT) revealed an ectopically positioned impacted maxillary canine with unfavorable angulation and inadequate eruption trajectory. The impacted tooth demonstrated close proximity to adjacent structures, while available orthodontic space and axial orientation were considered unfavorable for conventional orthodontic traction. No significant cystic lesion or advanced root resorption of adjacent teeth was identified.

Diagnosis

Based on the clinical and radiographic findings, the following diagnosis was established:

- Impacted permanent maxillary canine
- Retained primary canine
- Ectopic eruption pathway with unfavorable angulation
- Limited feasibility and poor prognosis for orthodontic repositioning

Treatment Planning

A multidisciplinary treatment plan involving oral surgery and endodontic management was developed. After evaluation of the anatomical limitations and anticipated orthodontic complexity, intentional reimplantation was selected as the most appropriate tooth-preserving treatment option.

The planned procedure consisted of the following stages:

1. Surgical exposure and atraumatic extraction of the impacted canine
2. Extraoral endodontic treatment under sterile conditions
3. Conservative preparation of the recipient socket
4. Immediate reimplantation of the treated canine
5. Semi-rigid splint stabilization during the healing phase

This treatment approach was selected based on previously reported biological principles and clinical outcomes associated with intentional reimplantation and tooth autotransplantation procedures, particularly in cases where orthodontic repositioning is considered difficult or unpredictable.

Surgical Procedure

Atraumatic Surgical Extraction

The procedure was performed under local anesthesia using a minimally traumatic surgical approach. Following mucoperiosteal flap elevation and conservative bone exposure, the impacted canine was carefully luxated and extracted while minimizing injury to the surrounding alveolar bone and periodontal ligament.

Special attention was directed toward preservation of root surface integrity and maintenance of viable periodontal ligament cells, which are considered essential for periodontal healing and prevention of ankylosis or inflammatory root resorption. Mechanical trauma to the cementum surface was avoided as much as possible throughout the extraction procedure. Immediately after extraction, the tooth was maintained in a moist environment using sterile saline solution in order to prevent desiccation of periodontal ligament tissues.

Extraoral Endodontic Treatment

Extraoral root canal treatment was performed

immediately following extraction under sterile operative conditions. Cleaning and shaping of the root canal system were completed using conventional endodontic instrumentation techniques, followed by obturation with gutta-percha in teeth demonstrating complete root formation.

Strict aseptic control was maintained during the entire extraoral phase to minimize the risk of bacterial contamination. Particular emphasis was placed on limiting extraoral manipulation time because prolonged exposure of the periodontal ligament has been associated with reduced cellular viability and increased risk of replacement resorption and ankylosis.

According to existing evidence from reimplantation and autotransplantation literature, preservation of periodontal ligament vitality is strongly correlated with minimized extraoral time. Therefore, all surgical and endodontic procedures were performed in a controlled and time-efficient manner, with continuous hydration of the root surface using sterile saline solution throughout the procedure. Reimplantation was completed as rapidly as clinically feasible to optimize periodontal healing potential.

Recipient Site Preparation

The recipient site was prepared using the socket of the retained primary canine with minimal surgical modification. Conservative osteotomy was performed only when necessary to facilitate appropriate positioning and passive adaptation of the reimplanted tooth. Care was taken to preserve surrounding alveolar bone architecture and vascular integrity while avoiding excessive curettage or compression of the socket walls. Maintenance of an adequate blood supply within the recipient site was considered important for periodontal ligament reattachment and early healing.

Reimplantation Procedure

Following completion of endodontic treatment and recipient site preparation, the impacted canine was carefully repositioned into the prepared socket with correct axial orientation and controlled insertion pressure. The tooth was seated passively to minimize additional trauma to the periodontal ligament and to facilitate adaptation between the root surface and surrounding alveolar bone. Immediate primary stability was achieved clinically without excessive force or additional fixation procedures.

Correct occlusal relationship and axial positioning were verified before stabilization.

Splint Stabilization

Semi-rigid splinting was performed using flexible orthodontic wire and composite resin. The splint was designed to provide adequate stabilization while allowing limited physiological micromovement during the healing phase. Functional semi-rigid stabilization has been reported to support periodontal ligament repair and reduce the likelihood of ankylosis compared with rigid fixation techniques. The splint remained in place for the planned postoperative stabilization period according to clinical mobility and periodontal healing.

Postoperative Management and Follow-Up

Postoperative instructions included maintenance of oral hygiene, soft diet recommendations, chlorhexidine mouth rinse, and antibiotic therapy when indicated. Patients were advised to avoid excessive functional loading during the early healing phase.

Immediate Postoperative Findings

Clinical examination immediately after surgery demonstrated:

- Stable positioning of the reimplanted canine
- Absence of active bleeding or displacement
- Satisfactory primary stability
- Acceptable occlusal relationship

No immediate postoperative complications were observed.

Ten-Day Follow-Up

At the 10-day postoperative review, the following findings were recorded:

- Intact semi-rigid splint
- Favorable gingival healing
- Absence of infection or suppuration
- No abnormal tooth mobility
- Satisfactory soft tissue adaptation

The patient remained asymptomatic during this period.

Three-Month Follow-Up

Clinical and radiographic examination performed after 3 months demonstrated favorable periodontal healing and functional stability of the reimplanted canine.

The following observations were identified:

- Stable periodontal condition
- Absence of clinical signs of ankylosis
- No evidence of inflammatory root resorption
- Healthy gingival adaptation
- Functional integration within the dental arch

Radiographic evaluation demonstrated preservation of the periodontal ligament space and favorable early bone healing without pathological radiolucency. Figures 1–8 illustrate the sequence of the presented clinical case.



Figure 1.a,b Preoperative CBCT imaging demonstrating ectopic impaction and unfavorable angulation of the maxillary canine

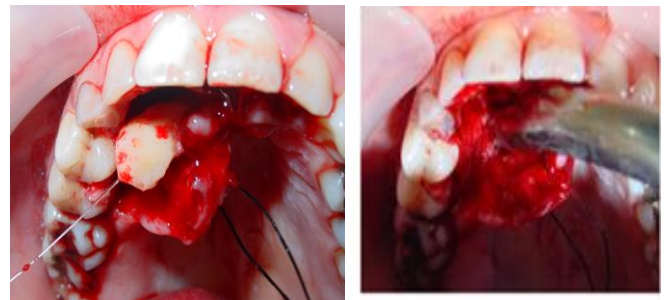


Figure 2.a,b Atraumatic surgical extraction of impacted canine



Figure 3. Extraoral endodontic treatment and immediate reimplantation of the canine into the recipient socket.

Figure 6. Semi-rigid splint stabilization using flexible wire and composite resin

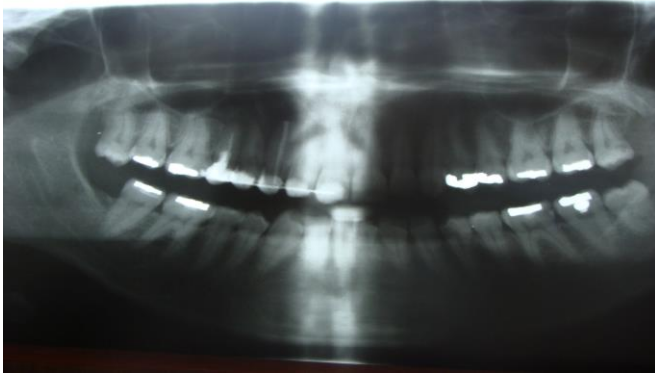


Figure 7. Immediate postoperative radiographic evaluation demonstrating correct positioning of the reimplanted canine.

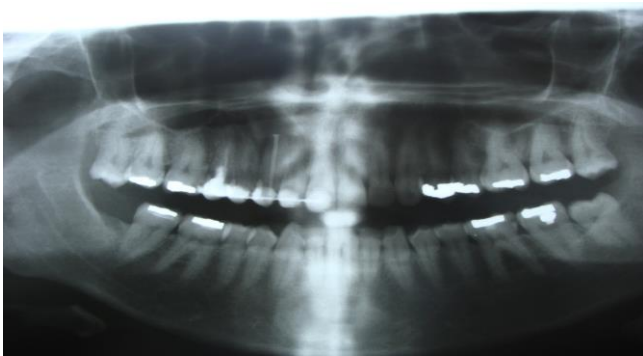


Figure 8. Postoperative radiographic control at 10 days demonstrating satisfactory periodontal adaptation.

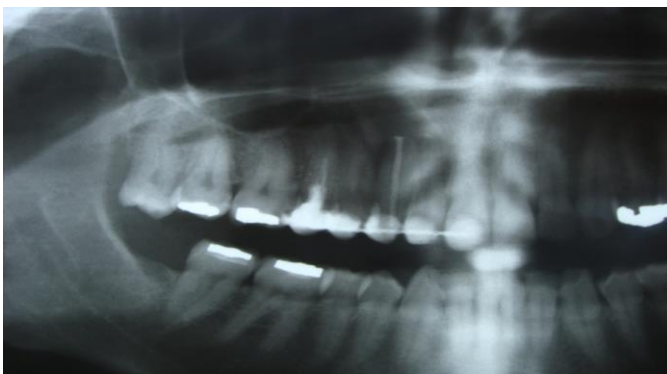


Figure 9. Clinical and radiographic follow-up after 3 years demonstrating functional stability and favorable periodontal healing.

3. RESULTS

A total of 24 patients presenting with impacted maxillary canines underwent surgical extraction followed by intentional reimplantation using a standardized atraumatic surgical and endodontic protocol. All procedures were completed successfully without intraoperative complications, and no surgical interventions required modification or discontinuation. Immediate primary stability was achieved in all cases at the time of reimplantation, allowing satisfactory positioning of the canine within the recipient socket.

Clinical examination confirmed acceptable axial alignment, favorable occlusal relationships, and adequate adaptation of surrounding soft tissues immediately after surgery. The postoperative healing period was generally uneventful. All patients attended scheduled clinical and radiographic follow-up visits and were available for outcome assessment. Throughout the observation period, reimplanted teeth demonstrated favorable biological responses with preservation of function and satisfactory integration within the dental arch.

3.1 Survival and Clinical Outcomes

Clinical and radiographic outcomes were assessed according to predefined success criteria established before analysis. Tooth survival was defined as retention of the reimplanted canine within the oral cavity throughout the follow-up period regardless of the presence of minor non-progressive complications. All 24 reimplanted maxillary canines remained present and functional during follow-up, resulting in a survival rate of 100%. No tooth required extraction, replacement, or additional surgical intervention because of treatment failure.

Clinical success was defined according to the following criteria:

- Functional tooth stability with mobility Grade 0 or Grade I.
- Absence of progressive inflammatory or replacement root resorption.
- Absence of clinical or radiographic ankylosis.
- Satisfactory periodontal health and soft tissue adaptation.
- Maintenance of functional and esthetic integration within the dental arch.

Twenty-two of the 24 reimplanted canines fulfilled all success criteria, corresponding to a clinical success rate of 91.7%. One patient (4.2%) demonstrated mild non-progressive external root resorption detected radiographically during follow-up. Another patient (4.2%) exhibited persistent Grade I mobility without evidence of pain, periodontal deterioration, infection, or functional impairment. These two cases were categorized as partial clinical successes because minor complications were present despite preservation of tooth function and retention. Importantly, no cases of ankylosis, severe mobility, progressive root resorption, infection, periodontal breakdown, or tooth loss were observed. Radiographic examinations demonstrated preservation of periodontal ligament integrity and stable alveolar bone support in the majority of cases. Because of the limited sample size and absence of

treatment failures, inferential statistical analyses and survival modeling were not considered appropriate. Therefore, all outcomes are presented descriptively.

Table 4. Survival and Overall Clinical Outcomes (n = 24)

Outcome Parameter	Number of Cases	Percentage
Complete clinical success	22	91.7%
Partial clinical success	2	8.3%
Tooth survival/retention	24	100%
Tooth loss	0	0%
Ankylosis	0	0%
Progressive root resorption	0	0%
Infection	0	0%

3.2 Clinical Findings

Clinical follow-up examinations demonstrated favorable periodontal healing and functional adaptation in most patients. The reimplanted canines maintained satisfactory integration within the dental arch with healthy surrounding soft tissues and absence of clinically significant inflammatory complications.

Mobility Assessment

Tooth mobility was evaluated using the modified Miller mobility classification system during follow-up examinations.

Twenty-two patients (91.7%) demonstrated physiological mobility corresponding to Grade 0 mobility. Two patients (8.3%) exhibited Grade I mobility. No cases demonstrated Grade II or Grade III mobility. The two teeth presenting with Grade I mobility remained clinically stable throughout the observation period and did not show progressive deterioration or associated periodontal pathology.

No patient exhibited traumatic occlusion, excessive mobility, discomfort during function, or evidence of loss of periodontal support.

Periodontal Findings

Periodontal evaluation included assessment of gingival adaptation, probing depth measurements, bleeding on probing, suppuration, and general periodontal health. The periodontal condition remained favorable throughout follow-up. Probing depths were generally

within normal physiological limits and did not exceed 3 mm around the reimplanted teeth. No bleeding on probing or suppuration was observed. Gingival tissues demonstrated healthy contour, color, and adaptation, and no evidence of progressive attachment loss was detected. Soft tissue healing was uneventful in most patients, with maintenance of satisfactory mucogingival integration throughout the observation period.

Functional Stability

All reimplanted canines remained functional throughout follow-up. Occlusal stability and acceptable esthetic integration were maintained in every patient. Functional loading was tolerated without evidence of discomfort or progressive mobility. No patient reported persistent pain, masticatory difficulties, speech impairment, or esthetic dissatisfaction related to the treated tooth. Overall, the clinical findings indicated stable periodontal adaptation and favorable functional integration following intentional reimplantation.

Functional Stability

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Table 5. Clinical Findings During Follow-Up (n = 24)

Clinical Parameter	Number of Cases	Percentage
Grade 0 mobility	22	91.7%
Grade I mobility	2	8.3%
Grade II mobility	0	0%
Grade III mobility	0	0%
Healthy gingival adaptation	24	100%
Bleeding on probing	0	0%
Suppuration	0	0%
Functional tooth retention	24	100%

3.3 Radiographic Findings

Radiographic assessment was performed using serial

periapical radiographs and cone-beam computed tomography when clinically indicated.

Radiographic evaluation demonstrated preservation of periodontal and alveolar structures in most cases. Favorable healing patterns were observed, including maintenance of periodontal ligament space continuity and stable surrounding bone architecture.

The majority of patients demonstrated a continuous periodontal ligament space and preservation of lamina dura integrity around the reimplanted roots. Alveolar bone levels remained stable, and no significant marginal bone loss was observed.

One patient (4.2%) demonstrated mild external root resorption. The defect remained superficial and non-progressive throughout the follow-up period and was not associated with clinical symptoms or functional impairment. No cases demonstrated moderate or severe inflammatory root resorption, replacement resorption, or circumferential resorption patterns.

Importantly, radiographic evidence of ankylosis was not identified in any patient.

Table 6. Radiographic Findings (n = 24)

Radiographic Finding	Number of Cases	Percentage
Preserved periodontal ligament space	23	95.8%
Intact lamina dura	23	95.8%
Stable alveolar bone levels	24	100%
Mild external root resorption	1	4.2%
Moderate or severe root resorption	0	0%
Radiographic ankylosis	0	0%

3.4 Postoperative Complications

Postoperative complications were limited and remained clinically manageable throughout the observation period. Most patients experienced uneventful healing without significant adverse events. Only two minor complications were identified during follow-up.

One patient demonstrated mild external root resorption, while one patient exhibited persistent Grade I mobility. Both findings remained stable and non-progressive throughout follow-up and did not compromise function or tooth retention.

No patient developed postoperative infection,

suppuration, abscess formation, progressive root resorption, ankylosis, severe mobility, periodontal breakdown, or delayed tooth loss.

Importantly, none of the observed complications required extraction of the reimplanted tooth or additional corrective surgical intervention.

Table 7. Postoperative Complications (n = 24)

Complication	Number of Cases	Percentage
No complications	22	91.7%
Mild external root resorption	1	4.2%
Persistent Grade I mobility	1	4.2%
Infection	0	0%
Ankylosis	0	0%
Tooth loss	0	0%

3.5 Follow-Up Outcomes

The duration of follow-up ranged from the immediate postoperative period to a maximum of three years depending on patient availability and recall attendance. Throughout the observation period, all reimplanted canines remained retained within the dental arch and continued to function satisfactorily.

Clinical and radiographic follow-up examinations consistently demonstrated stable periodontal healing, preservation of supporting alveolar bone, favorable soft tissue adaptation, and maintenance of functional occlusal relationships. No delayed extractions, catastrophic failures, or progressive pathological changes were observed.

The biological response observed following intentional reimplantation was generally favorable and suggested successful periodontal adaptation under controlled surgical conditions.

Although longer follow-up periods remain necessary to evaluate the potential development of delayed complications such as ankylosis or replacement resorption, the present findings indicate that intentional reimplantation of impacted maxillary canines may provide predictable short- and intermediate-term outcomes when appropriate biological and surgical principles are carefully followed.

Table 8. Overall Follow-Up Outcomes (n = 24)

Outcome Parameter	Result
Total number of patients	24
Clinical success	22 (91.7%)
Partial clinical success	2 (8.3%)
Functional tooth retention	24 (100%)
Primary stability at reimplantation	24 (100%)
Infection	0 (0%)
Ankylosis	0 (0%)
Mild external root resorption	1 (4.2%)
Severe root resorption	0 (0%)
Tooth loss	0 (0%)

4. DISCUSSION

Intentional reimplantation is a biologically sensitive surgical procedure that depends primarily on preservation of periodontal ligament (PDL) vitality and minimization of mechanical trauma during tooth extraction, handling, and reinsertion^{19,22,35}. Historically, the technique was regarded as a treatment of last resort because of concerns regarding ankylosis, inflammatory root resorption, and long-term instability. However, advances in atraumatic extraction techniques, microsurgical procedures, endodontic management, and understanding of periodontal wound healing have renewed interest in intentional reimplantation as a conservative tooth-preserving treatment option, particularly in situations where orthodontic traction is not feasible or is associated with a poor prognosis^{20,23,25,37–40}.

The present retrospective case series evaluated the clinical and radiographic outcomes of intentional reimplantation of impacted maxillary canines performed according to standardized biological and surgical protocols. Clinical success was achieved in 22 of 24 patients (91.7%), while all reimplanted canines remained functional and retained throughout follow-up, resulting in an overall tooth survival rate of 100%. These findings indicate that impacted maxillary canines can remain biologically stable and functionally integrated following intentional reimplantation when appropriate surgical principles are carefully respected.

One of the most important determinants of successful intentional reimplantation is preservation of viable periodontal ligament cells. Andreasen and Kristerson demonstrated that damage to the periodontal ligament during extraction or prolonged extraoral exposure significantly increases the risk of replacement resorption and ankylosis following replantation

procedures⁴¹. Subsequent investigations have confirmed that periodontal ligament vitality directly influences cementum repair, periodontal regeneration, and re-establishment of functional attachment between the root surface and surrounding alveolar bone^{42–44}. The periodontal ligament contains fibroblasts, progenitor cells, vascular structures, and collagen fibers that are essential for periodontal healing and long-term tooth stability.

For this reason, atraumatic extraction represented a critical component of the surgical protocol used in the present study. Excessive luxation forces, unnecessary manipulation of the root surface, curettage of the periodontal ligament, and desiccation were carefully avoided. Continuous hydration of the extracted tooth with sterile saline solution was maintained throughout the extraoral phase to preserve cellular viability and reduce the risk of postoperative complications. Similar recommendations have been emphasized in studies evaluating tooth autotransplantation, traumatic tooth avulsion, and intentional reimplantation procedures^{26,29,45,46}.

Another important prognostic factor is minimization of extraoral time. Experimental and clinical studies have demonstrated that prolonged extraoral exposure markedly decreases survival of periodontal ligament cells and increases the likelihood of inflammatory and replacement root resorption^{28,33,47–49}. Consequently, all surgical and endodontic procedures in the present series were organized to minimize extraoral manipulation and facilitate immediate reinsertion of the tooth following completion of root canal treatment and recipient site preparation. Maintenance of root surface hydration combined with reduction of extraoral time likely contributed to the favorable healing outcomes observed in this study.

The role of endodontic management in intentional reimplantation remains an important clinical consideration. In teeth with complete root development and closed apices, pulpal revascularization is unlikely following reimplantation, making root canal treatment necessary to prevent pulpal necrosis and inflammatory complications^{20,50,51}. In the present series, extraoral root canal treatment was performed under sterile conditions before reinsertion whenever indicated. This approach allowed elimination of potential endodontic infection while avoiding the need for additional postoperative intervention. No cases of postoperative infection, periapical pathology, or inflammatory complications were identified during follow-up.

Semi-rigid splinting was used in all patients to provide stabilization during the initial healing period while

permitting limited physiological movement. Previous studies have suggested that rigid fixation may increase the risk of ankylosis because functional stimulation of the periodontal ligament is reduced^{52,53}. In contrast, semi-rigid stabilization appears to support periodontal healing and regeneration while maintaining adequate tooth stability. Splints were maintained for approximately two to four weeks depending on the degree of primary stability and clinical healing. No clinical or radiographic evidence of ankylosis was detected during follow-up, which may be related to the stabilization protocol employed.

Radiographic outcomes were generally favorable. Preservation of periodontal ligament space and lamina dura continuity was observed in most cases, suggesting maintenance of periodontal attachment and successful alveolar bone healing. Stable alveolar bone support was evident throughout the observation period. Only one patient demonstrated mild external root resorption, which remained superficial and non-progressive without clinical symptoms or functional impairment. Importantly, no cases of severe inflammatory root resorption, replacement resorption, or radiographic ankylosis were identified. These findings support previous observations indicating that careful preservation of periodontal ligament vitality and atraumatic handling significantly reduce the incidence of postoperative complications^{19,20,30,31}.

The clinical outcomes reported in the present study compare favorably with findings from previous investigations involving intentional reimplantation and tooth autotransplantation. Mainkar reported high survival rates for teeth treated using contemporary intentional replantation protocols²⁵. Similarly, Jang et al. demonstrated favorable long-term outcomes for intentionally replanted teeth followed for up to eleven years, with survival rates exceeding 90%³². Long-term investigations by Czochrowska and colleagues reported survival rates ranging from approximately 79% to 90% for transplanted teeth when atraumatic surgical techniques and appropriate case selection were applied^{40,54}. The 91.7% clinical success rate and 100% tooth survival observed in the present study therefore fall within the upper range of previously reported outcomes and further support the effectiveness of intentional reimplantation when modern biological principles are strictly followed.

A notable strength and novel aspect of the present investigation is its specific focus on impacted maxillary canines. Most published studies evaluating intentional reimplantation have primarily involved teeth with endodontic pathology, periodontal involvement, root fractures, or complex root anatomy. In contrast,

evidence regarding intentional reimplantation of impacted maxillary canines remains limited and is largely restricted to isolated case reports and small case series^{20,22,23,25}. The present study contributes additional clinical and radiographic evidence from a cohort of 24 patients treated using a standardized surgical and endodontic protocol with follow-up extending up to five years. To the authors' knowledge, few studies have reported outcomes for a comparable number of intentionally reimplanted impacted maxillary canines using a uniform treatment approach. These findings therefore provide meaningful clinical data supporting intentional reimplantation as a potential treatment option in selected impacted canine cases with an unfavorable orthodontic prognosis.

Intentional reimplantation should be considered within the broader context of available treatment options for impacted maxillary canines. Surgical exposure followed by orthodontic traction remains the preferred treatment approach because it preserves the natural periodontal attachment and facilitates eruption of the impacted tooth into the dental arch^{14,15,56,57}. Nevertheless, orthodontic treatment may be contraindicated or associated with poor prognosis in cases involving severe displacement, excessive angulation, ankylosis, root dilaceration, proximity to adjacent roots, or anticipated prolonged treatment duration¹⁶⁻¹⁸. In such situations, intentional reimplantation may provide a valuable alternative that allows preservation of the natural tooth while avoiding extraction and prosthetic replacement.

Compared with extraction followed by implant placement or fixed prosthetic rehabilitation, intentional reimplantation offers several biological advantages. Preservation of the patient's own tooth contributes to maintenance of alveolar bone volume, periodontal proprioception, gingival architecture, and esthetic integration^{29,34,40}. These advantages are particularly relevant in adolescent and young adult patients, where implant placement may be complicated by ongoing skeletal growth and long-term esthetic concerns. Maintenance of the natural canine may therefore represent a desirable treatment objective whenever feasible.

Despite the encouraging findings, several limitations of the present study should be acknowledged. The retrospective design inherently limits control over patient selection, treatment standardization, and follow-up consistency. The sample size was relatively small, reducing statistical power and limiting generalizability of the results. Variability in impaction depth, angulation, root morphology, and follow-up duration may also have influenced treatment outcomes. In

addition, standardized patient-reported outcome measures and detailed periodontal indices were not available for all cases.

Another limitation relates to follow-up duration. Although some patients were monitored for up to five years, longer observation periods remain necessary to evaluate late complications such as ankylosis, replacement resorption, and progressive periodontal breakdown, which may develop several years after treatment^{28,55}. Future prospective multicenter investigations involving larger patient populations and standardized protocols are required to identify prognostic variables associated with treatment success and to further clarify long-term predictability.

From a clinical perspective, the present findings suggest that intentional reimplantation may serve as a useful adjunctive or salvage procedure in carefully selected patients with impacted maxillary canines that are unsuitable for orthodontic traction. Successful outcomes require comprehensive treatment planning and close collaboration among oral surgeons, endodontists, orthodontists, and restorative clinicians. Thorough radiographic evaluation using CBCT, careful surgical planning, preservation of periodontal ligament vitality, minimization of extraoral time, appropriate endodontic management, and physiologic splinting appear to be fundamental factors contributing to favorable healing and long-term tooth retention.

DECLARATIONS

Conflict of Interest

The author declare no conflict of interest.

Funding

No external funding was received for this study.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki for research involving human subjects.

Written informed consent for treatment and the use of anonymized clinical and radiographic data for scientific publication was obtained from all patients or their legal guardians.

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REVIEW ARTICLE

CONTEMPORARY PERIODONTAL PLASTIC SURGERY FOR GINGIVAL RECESSION: A NARRATIVE REVIEW OF EVIDENCE AND LONG-TERM CLINICAL OUTCOMES

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Abstract

Background: Gingival recession is a prevalent mucogingival condition characterized by the apical displacement of the gingival margin beyond the cemento-enamel junction (CEJ), resulting in root surface exposure. This condition is associated with esthetic concerns, dentin hypersensitivity, root caries, and increased plaque retention. Advances in periodontal plastic surgery, microsurgical techniques, and regenerative biomaterials have significantly enhanced the predictability and outcomes of root coverage procedures.

Although many consider gingival recession to be a cosmetic problem, there is a critically important factor to consider. The connective tissue to which the gingiva is attached is the only tissue that prevents bacterial infiltration and therefore plays a crucial role in maintaining periodontal support.

Objective: This narrative review aims to critically summarize current evidence on the etiology, classification, and contemporary surgical management of gingival recession, with particular emphasis on periodontal plastic surgical techniques and regenerative approaches.

Methods: A literature review was conducted using PubMed, Scopus, Web of Science, and Google Scholar. Articles published between 2000 and 2025 were included if they evaluated surgical management of gingival recession. The review incorporated randomized controlled trials, systematic reviews, and key landmark studies.

Results: Coronally advanced flap (CAF) combined with subepithelial connective tissue graft (SCTG) remains the most predictable approach for root coverage, demonstrating high success rates and long-term stability. Tunnel techniques offer excellent esthetic outcomes with reduced surgical morbidity and minimal scarring. Biomaterials such as collagen matrices and acellular dermal matrices represent viable alternatives in selected cases, primarily by eliminating donor-site morbidity, although their predictability remains lower compared with autogenous grafting techniques.

Conclusion: Contemporary periodontal plastic surgery provides reliable and predictable treatment options for gingival recession, particularly in Miller Class I and II defects. Treatment success depends on accurate diagnosis, appropriate case selection, gingival phenotype, vascular supply, and meticulous surgical technique. Future advances in tissue engineering, biologically active materials, and minimally invasive surgical techniques may further improve clinical outcomes while reducing patient morbidity.

INTRODUCTION

Gingival recession is one of the most common mucogingival deformities encountered in clinical periodontology and is defined as the apical displacement of the gingival margin beyond the cemento-enamel junction (CEJ), resulting in exposure of the root surface^{1,2}.

The condition may affect single or multiple teeth and is commonly associated with esthetic concerns, dentin hypersensitivity, root caries, cervical abrasion, and increased plaque accumulation.^{3,4} In addition functional complications, gingival recession may negatively

influence patient comfort and smile esthetics, particularly in the anterior region.

Epidemiological studies indicate that gingival recession affects a substantial proportion of the adult population, with prevalence and severity increasing progressively with age.¹⁴ Growing patient awareness of dentofacial esthetics and periodontal health has significantly increased the demand for predictable root coverage procedures and minimally invasive periodontal plastic surgery. As a result, management of gingival recession has become an important component of contemporary

mucogingival therapy. According to the 2017 World Workshop classification developed by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP), gingival recession is classified among mucogingival deformities and conditions.⁵ Clinically, recession defects are frequently associated with thin periodontal phenotype, alveolar bone dehiscence, shallow vestibular depth, reduced width of keratinized tissue, and unfavorable tooth positioning.^{7,14}

These anatomical characteristics may significantly influence both disease progression and treatment predictability. The etiology of gingival recession is considered multifactorial. Several contributing factors have been identified, including traumatic tooth brushing, periodontal inflammation, anatomical predisposition, orthodontic tooth movement, occlusal stress, and iatrogenic factors related to restorative or periodontal procedures.^{12,14,27} Among these, traumatic brushing and thin gingival phenotype are consistently reported as major risk factors associated with localized recession defects.^{14,27}

Miller's classification system remains one of the most widely used clinical methods for evaluating recession defects and estimating the potential for complete root coverage.^{6,11}

However, more recent classification systems incorporating interproximal attachment loss and periodontal phenotype have improved the diagnostic understanding of recession defects and treatment prognosis.³ Over recent decades, periodontal plastic surgery has evolved considerably from traditional mucogingival procedures toward microsurgical and regenerative approaches designed to improve wound stability, vascular supply, esthetic integration, and patient-centered outcomes.^{8,23,28}

Contemporary treatment modalities include coronally advanced flap (CAF), subepithelial connective tissue grafting (SCTG), tunnel techniques, free gingival grafts, and biomaterial-based therapies such as collagen matrices and acellular dermal substitutes.^{16,20,21,23} These techniques have substantially improved the predictability of root coverage procedures, particularly in Miller Class I and II recession defects. Despite significant clinical advances, complete and stable root coverage remains challenging in cases involving deep recession defects, interproximal attachment loss, reduced vestibular depth, or unfavorable tooth anatomy.^{6,19} In addition, long-term success is strongly influenced by patient-related and site-specific factors including gingival phenotype, oral hygiene, smoking status, and surgical technique.^{14,29,32} Therefore, careful diagnosis, proper case selection, and evidence-based surgical planning are essential for achieving stable functional and esthetic outcomes.

The aim of this narrative review is to critically evaluate current evidence regarding the etiology, classification, and surgical management of gingival recession, with particular emphasis on periodontal plastic surgical procedures, regenerative biomaterials, and factors affecting long-term treatment predictability.

2. MATERIALS AND METHODS

This study was designed as a structured narrative review. The objective was to synthesize and critically appraise the available literature on periodontal plastic surgical management of gingival recession, rather than to conduct a systematic review or meta-analysis. An electronic literature search was performed using the following databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Google Scholar

The search focused on publications addressing gingival recession and periodontal plastic surgery. Relevant studies were identified using a keywords including:

- “gingival recession”
- “periodontal plastic surgery”
- “root coverage”
- “coronally advanced flap”
- “subepithelial connective tissue graft”
- “tunnel technique”
- “collagen matrix”
- “guided tissue regeneration”

The search was limited to articles published in English between 2000 and 2025. The initial search identified 324 records. After removal of duplicates and screening of titles and abstracts, 87 articles were reviewed in full text and 46 studies were included in the final narrative synthesis.

3. RESULTS

The selected publications were reviewed and synthesized to evaluate the current evidence regarding the etiology, surgical management, regenerative approaches, and prognostic determinants associated with gingival recession therapy. The included literature consisted primarily of randomized controlled clinical trials, systematic reviews, longitudinal clinical investigations, and landmark studies in periodontal plastic surgery and mucogingival therapy. For clarity, the findings were organized into four major thematic areas: (1) etiology and risk profile, (2) comparative effectiveness of surgical techniques, (3) biomaterials and regenerative approaches, and (4) prognostic factors influencing treatment outcomes.

3.1 Etiology and Risk Profile

The reviewed literature confirms that gingival recession is a multifactorial condition influenced by anatomical, traumatic, inflammatory, and behavioral factors.^{2,14,22} Among the anatomical characteristics most frequently associated with recession development are thin gingival phenotype, reduced width of keratinized tissue, shallow vestibular depth, and prominent root anatomy.^{2,30}

These factors appear to increase tissue susceptibility to mechanical trauma and compromise long-term periodontal stability. Traumatic tooth brushing remains the etiologic factor most consistently associated with localized recession defects.²⁷

Excessive brushing force, improper brushing technique, and use of hard-bristled toothbrushes have all been implicated in the initiation and progression of soft tissue recession. The role of orthodontic tooth movement and occlusal trauma remains less clearly defined. Although these factors may contribute to recession development under certain clinical conditions, most studies consider them secondary or modifying influences rather than primary etiologic causes.^{14,30}

Periodontal inflammation also plays an important role by accelerating soft tissue breakdown and impairing periodontal support.²²

Table 1. Etiologic Factors and Level of Consensus in the Literature

Etiologic Factor	Role in Recession	Level of Agreement in Literature
Traumatic tooth brushing	Primary initiating factor	High consensus
Thin gingival phenotype	Predisposing factor	High consensus
Reduced keratinized tissue width	Predisposing factor	High consensus
Shallow vestibular depth	Contributing factor	High consensus
Orthodontic tooth movement	Secondary/modifying factor	Moderate consensus
Occlusal trauma	Controversial contributor	Low–moderate consensus
Periodontal inflammation	Disease-modifying factor	High consensus

3.2 Comparative Effectiveness of Surgical Techniques

Among the available root coverage procedures, coronally advanced flap (CAF) combined with subepithelial connective tissue grafting (SCTG) consistently demonstrates the highest level of predictability and long-term clinical stability.^{4,16,31,47} Numerous clinical studies have reported superior root coverage outcomes, significant increases in gingival thickness, and enhanced soft-tissue stability when this technique is employed. The favorable biological response associated with SCTG is largely attributed to its ability to improve vascularization and reinforce the gingival phenotype. Furthermore, long-term follow-up investigations have shown that CAF combined with SCTG provides more stable results and lower recurrence rates of recession compared with most alternative treatment modalities. The technique is therefore widely regarded as the reference standard against which newer root coverage procedures are evaluated. CAF alone remains an effective treatment option for shallow recession defects, particularly in patients presenting with a favorable gingival phenotype and an adequate width of keratinized tissue. However, its predictability decreases in cases involving a thin periodontal phenotype, reduced soft-tissue thickness, or advanced recession defects.^{4,16} Clinical outcomes achieved with CAF alone may also be more susceptible to long-term relapse because of the limited capacity for soft-tissue augmentation. Tunnel-based procedures have gained increasing popularity because of their minimally invasive nature and superior esthetic integration. These techniques preserve papillary integrity, minimize surgical trauma, and reduce postoperative scarring, making them particularly suitable for the treatment of multiple adjacent gingival recessions.^{26,33} Preservation of the interdental tissues also contributes to improved blood supply and enhanced wound healing. Nevertheless, treatment outcomes remain highly technique-sensitive, and complete root coverage is not always achieved as consistently as with connective tissue graft–based procedures.^{7,21} Biomaterial-based approaches, including collagen matrices and acellular dermal matrices, offer the important advantage of eliminating donor-site morbidity and reducing patient discomfort associated with graft harvesting. These materials may represent valuable alternatives when autogenous donor tissue is limited or when patients prefer less invasive treatment options. However, the majority of available evidence indicates that their long-term predictability and stability remain inferior to those achieved with autogenous connective tissue grafting.^{20,22} Consequently, connective tissue grafts continue to be considered the most reliable option for achieving optimal root coverage and durable periodontal soft-tissue augmentation.

Table 2. Comparative Evidence of Root Coverage Techniques

Technique	Root Coverage Predictability	Esthetic Outcome	Morbidity	Long-term Stability	Evidence Consensus
CAF alone	Moderate–High	Moderate	Low	Moderate	High
CAF + SCTG	Very High	High	Moderate	Excellent	Very high consensus
SCTG alone	High	High	High	Excellent	High consensus
Tunnel technique	Moderate–High	Very High	Low	Good	Moderate consensus
Collagen matrix	Moderate	High	Very Low	Moderate	Moderate consensus
Acellular dermal matrix	Moderate	High	Low	Moderate	Moderate consensus
GTR / biologics	Variable	Moderate	Moderate	Variable	Low consensus

3.3 Biomaterials and Regenerative Approaches

The use of biomaterials and regenerative adjuncts has expanded considerably in contemporary periodontal plastic surgery. Several studies reported that collagen matrices and acellular dermal substitutes significantly reduce postoperative morbidity by eliminating the need for a palatal donor site.^{20,24}

These materials may improve patient comfort and shorten surgical time, particularly in cases requiring treatment of multiple recession defects.

Despite these advantages, the available evidence suggests that biomaterial-based procedures generally provide lower root coverage predictability compared with autogenous SCTG, especially in Miller Class I and II recession defects.^{20,24,32}

In addition, long-term tissue stability remains more favorable with connective tissue grafting procedures. Regenerative approaches such as guided tissue regeneration (GTR) and enamel matrix derivatives have shown variable clinical outcomes.^{15,28}

Although these techniques may enhance biologic healing and periodontal regeneration, their effectiveness appears to depend heavily on flap stability, defect morphology, surgical skill, and patient-related factors.²⁸

Current evidence does not consistently demonstrate superiority over conventional connective tissue grafting techniques.

Table 3. Summary of Biomaterials and Regenerative Strategies

Approach	Main Advantage	Main Limitation	Evidence Strength
Collagen matrix	No donor site morbidity	Lower predictability	Moderate
Acellular dermal matrix	Reduced morbidity	Cost and variability	Moderate
Guided tissue regeneration	Regenerative potential	Technique sensitivity	Low–moderate
Enamel matrix derivatives	Biological enhancement	Inconsistent outcomes	Moderate

3.4 Prognostic Factors Influencing Outcomes

Treatment outcomes in gingival recession therapy are strongly influenced by both patient-related and site-specific factors rather than surgical technique alone.^{2,14,31} The literature consistently identifies gingival phenotype, keratinized tissue width, interproximal attachment level, oral hygiene, smoking status, and defect morphology as major determinants of treatment success. A thick gingival phenotype and adequate keratinized tissue width are generally associated with improved wound stability and greater likelihood of complete root coverage. In contrast, smoking, poor plaque control, and interproximal attachment loss are consistently linked with reduced healing potential and compromised clinical outcomes.^{2,14,22} Mandibular anterior recession defects are often considered particularly challenging because of limited vestibular depth, shallow soft tissue dimensions, and increased muscular tension in this region.³¹ These anatomical limitations may negatively affect flap stability and long-term treatment predictability.

Table 4. Prognostic Factors Affecting Root Coverage Outcomes

Factor	Effect on Outcome	Level of Evidence Consensus
Thick gingival phenotype	Improves predictability	High
Adequate keratinized tissue	Improves stability	High
Intact interproximal attachment	Enables complete coverage	High
Smoking	Impairs healing	High
Poor oral hygiene	Reduces success	High
Mandibular anterior location	Reduces predictability	High
Interproximal attachment loss	Limits root coverage	High

3.5 Overall Synthesis of Evidence

The overall body of evidence demonstrates a relatively consistent hierarchy regarding the predictability of root coverage procedures. Coronally advanced flap combined with subepithelial connective tissue grafting remains the most reliable and well-documented approach for achieving stable long-term root coverage outcomes.^{16,20,24,31,47}

Connective tissue grafting alone and CAF alone may provide favorable results in selected cases, whereas tunnel techniques offer excellent esthetic integration but demonstrate greater variability in complete root coverage outcomes.

Biomaterial-based procedures and regenerative adjuncts remain valuable alternatives, particularly when reduction of donor-site morbidity is a primary concern. However, their long-term predictability generally remains lower than that achieved with autogenous connective tissue grafts.^{20,24}

Importantly, the reviewed studies consistently emphasize that successful clinical outcomes depend not only on the selected surgical technique but also on defect morphology, tissue phenotype, vascular supply, surgical execution, and patient compliance.^{2,14,31}

The present review also includes clinical case documentation with follow-up periods extending beyond 20 years, demonstrating the long-term stability of connective tissue grafting procedures. The first case illustrates successful root coverage and stable periodontal health following treatment of a localized recession defect.

The second case demonstrates long-term augmentation of keratinized tissue and maintenance of favorable restorative and periodontal conditions over time. Collectively, these cases support the long-term effectiveness and predictability of connective tissue-based periodontal plastic surgical procedures.

Clinical Case 1



Figure 1. Preoperative clinical presentation showing severe gingival recession on the upper right cuspid with absence of attached gingiva and marked vascularity at the gingival margin.



Figure 2. 2 vertical incisions, one on the mesial of the cuspid and a second one on the distal. Both incisions were at least 1mm away from the line angles of the tooth to prevent blood supply issues with the flap. Flap reflection demonstrating extensive fenestration and root exposure of 10mm's.



Figure 3. Placement of the connective tissue graft from the palatal donor site. The graft was stabilized with 5-0 chromic gut absorbable sutures.



Figure 4. Multiple 5-0 Chromic gut absorbable sutures were used to stabilize the flap. The connective tissue was 100% covered for primary closure.



Figure 5. One-year postoperative result demonstrating successful root coverage, improved gingival contour, and satisfactory esthetic healing.



Figure 6. Approximately 20-year postoperative follow-up showing stable periodontal health, continued coronal migration of the gingival margin, and shallow probing depths

Clinical Case 2



Figure 1. 1980's patient referred for periodontal evaluation. #18, #19, #20 and #21. The treatment plan is for provisionals to be placed on 318 and #19. Surgery to be undertaken using Biologic Shaping techniques. Visually one can see almost no Attached Gingiva as well as need for shaping of provisionalized teeth.



Figure 2. Outline of free gingival graft to be taken.

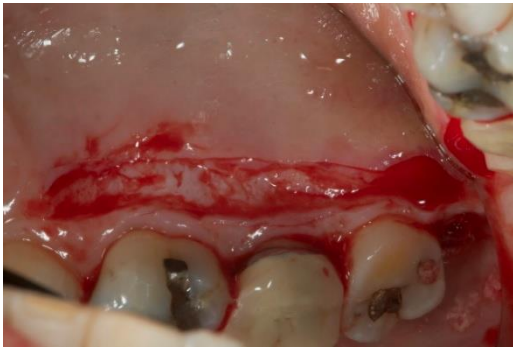


Figure 3. Graft removed using a #15 blade. Thickness of the graft is approximately 11/2mm's thick.

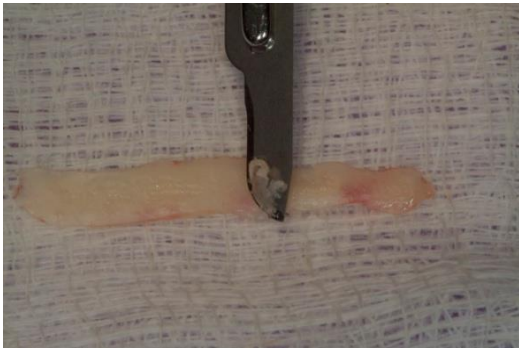


Figure 4. Removing the epithelium as part of the graft was to be placed under the reflected flap, the remaining portion to be placed at the margin of the bone.



Figure 5. Graft placed using 5-0 Chromic gut absorbable sutures attached to periosteum. The graft is now immovable.



Figure 6. Connective tissue covered in the posterior with flap. Both bicuspid had a margin connective tissue graft placed.



Figure 7. Approximately 20-year postoperative result demonstrating stable gingival tissues and healthy supragingival restorative margins with excellent long-term esthetics.

4. DISCUSSION

The present narrative review demonstrates the significant evolution of periodontal plastic surgery over recent decades, progressing from conventional mucogingival procedures toward minimally invasive and biologically driven approaches aimed at improving both functional and esthetic outcomes. Advances in microsurgical techniques, soft tissue management, and regenerative biomaterials have substantially improved the predictability of root coverage procedures and patient-centered treatment outcomes.

Among contemporary surgical procedures, coronally advanced flap (CAF) combined with subepithelial connective tissue grafting (SCTG) continues to demonstrate the highest level of predictability for complete root coverage and long-term tissue stability.^{4,16,31} Numerous clinical studies have reported favorable outcomes associated with SCTG, including increased gingival thickness, improved keratinized tissue width, enhanced vascularization, and long-term maintenance of soft tissue stability. Longitudinal observations have also described the phenomenon of “creeping attachment,” characterized by gradual coronal migration of the gingival margin after healing.^{16,31,46} Minimally invasive tunnel-based approaches have gained increasing popularity because they preserve papillary integrity and avoid vertical releasing incisions, thereby reducing postoperative morbidity and improving esthetic integration.^{23,33} These procedures are particularly advantageous in the management of multiple adjacent recession defects and in highly esthetic regions. However, despite favorable esthetic outcomes, the literature does not consistently demonstrate superior complete root coverage compared with CAF combined with connective tissue grafting.^{7,23} Furthermore, tunnel procedures are highly technique-sensitive and require advanced surgical experience to achieve predictable results. The introduction of biomaterial-based substitutes, including collagen

matrices and acellular dermal matrices, has expanded treatment possibilities in periodontal plastic surgery.^{21,24} These materials eliminate the need for a second surgical site and significantly reduce patient morbidity and postoperative discomfort. Nevertheless, most comparative studies indicate that autogenous connective tissue grafts continue to provide superior long-term predictability, particularly in advanced recession defects and thin periodontal phenotypes.^{20,24,32}

The limitations of CAF + SCTG should also be acknowledged. Although considered the current gold standard, the procedure requires harvesting autogenous connective tissue from the palate, which increases surgical complexity, operative time, and postoperative morbidity. Donor-site discomfort, bleeding, and delayed healing may negatively affect patient acceptance and satisfaction. In addition, the quantity of available donor tissue may be limited in patients requiring treatment of multiple recession defects. Economic considerations may further influence treatment selection, as advanced microsurgical procedures often require specialized instruments, increased clinical time, and operator expertise. Conversely, commercially available biomaterials may reduce surgical morbidity but are frequently associated with higher material costs and less predictable long-term outcomes.

Limitations associated with biomaterials include variable tissue integration, reduced volumetric stability, and inconsistent root coverage outcomes. Adjunctive regenerative approaches such as guided tissue regeneration (GTR) and enamel matrix derivatives have also been investigated as methods to enhance biologic healing and periodontal regeneration.^{15,28} Although these techniques may improve wound maturation and connective tissue attachment under favorable conditions, their clinical outcomes remain highly dependent on flap stability, defect morphology, blood supply, and surgical execution. Current evidence does not consistently demonstrate clear superiority over conventional connective tissue grafting procedures.²⁸

The reviewed literature further emphasizes that treatment outcomes are strongly influenced by patient-related and site-specific factors rather than surgical technique alone.^{2,14,22} Gingival phenotype, vestibular depth, interproximal attachment level, tooth position, smoking status, and oral hygiene are consistently reported as critical determinants of treatment success. Mandibular anterior recession defects remain particularly challenging because of limited vestibular depth, high muscle tension, and reduced soft tissue

thickness, all of which may compromise flap stability and healing.³¹

Several limitations of the present review should be acknowledged. As a narrative review, this study does not include quantitative meta-analysis or statistical synthesis of outcomes. In addition, heterogeneity among the included studies with respect to recession classification systems, surgical techniques, follow-up duration, and outcome assessment limits direct comparison between investigations.^{7,21}

Furthermore, long-term evidence supporting newer regenerative materials and biologic adjuncts remains limited when compared with the extensive evidence available for autogenous connective tissue grafting. Future research should focus on tissue engineering strategies, growth factor-based therapies, stem-cell applications, and development of next-generation biomaterials aimed at improving regenerative potential while minimizing patient morbidity.^{15,28} Additional well-designed randomized clinical trials with long-term follow-up are necessary to establish standardized protocols and evaluate long-term stability of contemporary regenerative approaches.

Overall, the current body of evidence supports coronally advanced flap combined with subepithelial connective tissue grafting as the gold standard for treatment of Miller Class I and II gingival recession defects because of its superior predictability, long-term stability, and favorable esthetic outcomes.^{16,31} Alternative minimally invasive and biomaterial-based approaches remain valuable in selected clinical situations, particularly when reduction of donor-site morbidity and improvement of patient comfort are important treatment considerations.

5. CONCLUSION

Gingival recession is a complex mucogingival condition that requires careful diagnosis and individualized treatment planning based on defect morphology, periodontal phenotype, and patient-related risk factors. Successful treatment outcomes depend not only on the selected surgical technique but also on accurate case selection, meticulous surgical execution, adequate plaque control, and long-term supportive periodontal maintenance.

Although minimally invasive and regenerative approaches continue to evolve and expand therapeutic possibilities, autogenous subepithelial connective tissue grafting remains the most predictable and well-documented method for achieving stable long-term root coverage and enhancement of periodontal soft tissue

quality. Contemporary periodontal plastic surgery should therefore combine evidence-based surgical principles with patient-specific treatment strategies in order to optimize both functional and esthetic outcomes.

Abbreviations

- **AAP** – American Academy of Periodontology
- **ADM** – Acellular Dermal Matrix
- **CAF** – Coronally Advanced Flap
- **CEJ** – Cementoenamel Junction
- **CTG / SCTG** – Connective Tissue Graft / Subepithelial Connective Tissue Graft

DECLARATIONS

Competing Interests

The authors declare no conflict of interest.

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Ethical Approval

Informed consent was obtained from all patients.

Retrospective clinical case documentation was reviewed and approved in accordance with ethical standards.

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INFLUENCE OF CLEAR ALIGNERS ON ORAL HEALTH AND MICROBIAL COMPOSITION DURING ORTHODONTIC TREATMENT: A NARRATIVE REVIEW

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Abstract

Objective: To critically evaluate current evidence regarding the effects of clear aligner therapy on periodontal health, oral microbiome composition, biofilm formation, and caries risk compared with fixed orthodontic appliances.

Materials and Methods: A narrative review informed by a structured literature search was conducted in PubMed, Scopus, Web of Science, and CNKI (2015–2025). Eligible studies included randomized controlled trials, cohort studies, observational studies, systematic reviews, and microbiological investigations. A total of 165 studies were identified, and 35 met the criteria for qualitative narrative synthesis.

Results: Evidence indicates that clear aligners are generally associated with more favorable short- and medium-term periodontal and hygiene-related indices, including reduced plaque accumulation and mild improvements in gingival bleeding compared with fixed appliances. Microbiome analyses suggest that aligners maintain relatively stable microbial diversity, although mild increases in cariogenic species may occur under poor oral hygiene compliance. Biofilm formation can occur on thermoplastic surfaces due to salivary pellicle deposition and microabrasion. Fixed appliances demonstrate a stronger association with microbial dysbiosis and enamel demineralization.

Conclusions: Clear aligner therapy offers more favorable periodontal and hygiene-related indices compared with fixed orthodontic appliances; however, the long-term clinical significance of these differences remains modest. Furthermore, these biological benefits are not automatic and depend greatly on patient compliance, individualized risk assessment, specific appliance designs, and dedicated hygiene protocols.

Keywords: clear aligners; orthodontics; oral microbiome; biofilm; periodontal health; caries risk

INTRODUCTION

Malocclusion is one of the most prevalent dental conditions globally and represents a major concern in orthodontic and periodontal practice due to its functional, esthetic, and psychosocial consequences^{1,2}. Orthodontic treatment aims to correct these discrepancies by achieving functional occlusion, improving facial esthetics, and enhancing patient well-being³.

However, orthodontic intervention inevitably influences the oral ecological system. Any orthodontic appliance may disrupt microbial homeostasis, leading to increased plaque accumulation, shifts in bacterial composition, and a higher risk of gingival inflammation and enamel demineralization⁴.

Fixed orthodontic appliances create retentive niches that promote plaque accumulation and hinder effective oral hygiene. Clinical studies consistently report increased plaque index, gingival inflammation, bleeding on probing, and enamel demineralization in patients undergoing fixed appliance therapy^{5–7}. These effects are mainly due to limited access for mechanical cleaning and enhanced bacterial colonization on orthodontic components⁸.

In contrast, clear aligners have emerged as an alternative orthodontic modality offering esthetic, functional, and biological advantages^{9–12}. Clear aligner systems such as Smartee and similar thermoplastic devices are removable and allow patients to maintain normal oral hygiene practices during treatment. Studies have demonstrated lower gingival inflammation and improved short-term

periodontal indices in patients treated with aligners, highlighting their favorable hygiene-related profile¹³⁻¹⁵.

Mechanistically, clear aligners introduce a distinct oral microenvironment. Unlike fixed appliances, aligners fully cover the dentition for approximately 18–22 hours per day, creating a sealed ecological niche. This continuous coverage may alter salivary flow dynamics, oxygen availability, and microbial adhesion patterns on tooth surfaces^{13,16,17}. Although aligners are removable, their prolonged wear time may still influence biofilm formation and microbial stability within the oral cavity^{14–18}.

Recent microbiological studies indicate that clear aligners have a relatively neutral effect on overall oral microbiome diversity. However, minor shifts in bacterial composition may occur during early treatment phases, particularly in patients with suboptimal oral hygiene. Increased levels of cariogenic bacteria such as *Streptococcus mutans* have been observed under poor compliance conditions¹⁹. Compared with fixed appliances, aligners tend to maintain a more stable microbial environment with fewer dysbiotic changes^{20,21}.

Biofilm formation on aligner surfaces represents an important clinical consideration. Surface microabrasions caused by mechanical wear, combined with salivary protein deposition, facilitate bacterial colonization over time. If cleaning protocols are insufficient, aligners may act as reservoirs for both cariogenic and periodontopathogenic bacteria²².

From a clinical perspective, clear aligners are generally associated with more favorable periodontal and hygiene-related indices compared to fixed appliances. Reduced plaque accumulation, lower gingival inflammation, and decreased bleeding on probing have been noted in multiple short-term clinical studies^{23,24}. However, these biological benefits are highly conditional and depend greatly on patient behavior, wear time, and cleaning habits.

In terms of white spot lesions and enamel demineralization, fixed appliances are associated with a higher incidence due to prolonged plaque retention around brackets. In contrast, aligners reduce this risk by allowing effective oral hygiene practices^{22,25}. However, the risk of true caries incidence and enamel demineralization may still increase if patients consume fermentable carbohydrates or sugary beverages while wearing aligners, or if the presence of numerous attachments and auxiliaries compromises the self-cleansing capacity of the dentition^{13,25}.

Comparative evidence between aligners and fixed appliances demonstrates differences in periodontal and hygiene-related outcomes. Fixed appliances are

superior in managing complex orthodontic cases requiring precise tooth movement and torque control, whereas aligners provide advantages in esthetics, hygiene control, and patient comfort^{14,26}. Therefore, treatment selection should be individualized based on malocclusion severity, biological response, and patient compliance. Despite increasing clinical evidence, limitations remain in the current literature. Many studies are short-term, in vitro, or heavily dependent on indirect microbiological data rather than long-term clinical trials. Standardized methodologies are required to improve comparability and strengthen evidence quality.

Overall, clear aligners represent a significant advancement in orthodontic therapy, offering more favorable periodontal and hygiene-related indices compared with fixed appliances^{16,23}. However, their biological advantages are not automatic. In real clinical practice, aligner therapy becomes biologically favorable only when combined with robust patient education, strict cleaning protocols, and careful tracking of attachments or auxiliaries that can impede routine hygiene²⁷.

This narrative review aims to critically evaluate the current evidence—categorizing insights from clinical, microbiological, and in vitro models—regarding periodontal outcomes, oral microbiome changes, and biofilm formation associated with clear aligner therapy compared with fixed orthodontic appliances.

To facilitate understanding of the clinical environment discussed throughout this review, Figure 1 illustrates a representative intraoral view of a patient undergoing clear aligner therapy. The image demonstrates the presence of thermoplastic aligners and composite attachments that are commonly used to improve the predictability and control of orthodontic tooth movement. These auxiliary elements are clinically relevant because they may influence plaque retention, oral hygiene accessibility, and biofilm accumulation, which are central topics addressed in the present review.



Figure 1. Clinical intraoral photograph illustrating clear aligner therapy with composite attachments

2. MATERIALS AND METHODS

2.1 Study Design

This study is a narrative review conducted using a structured and transparent literature search approach to summarize current evidence on the effects of clear aligner therapy on periodontal health, oral microbiome composition, biofilm formation, and caries risk in comparison with fixed orthodontic appliances. The review was designed to synthesize existing scientific literature rather than to perform a strict systematic review or meta-analysis. To maintain methodological clarity, we avoid full PRISMA compliance framing to match its narrative identity, while preserving a structured search architecture.

2.2 Literature Search Strategy

A comprehensive electronic search was conducted in the PubMed, Scopus, Web of Science, and CNKI databases covering the period from January 2015 to August 2025. The following keywords and their combinations were used: clear aligners, attachments, orthodontic appliances, oral microbiome, periodontal health, biofilm formation, gingivitis, Streptococcus mutans, and caries risk. Boolean operators (AND, OR) were applied to refine the search strategy. Additionally, manual screening of reference lists from relevant studies was performed to identify further eligible publications.

2.3 Study Selection and Data Extraction

All identified records were screened based on title and abstract relevance. Full-text articles were then assessed for eligibility. A total of 165 studies were initially identified. After removal of duplicates and exclusion of irrelevant or non-eligible studies, 35 studies were included in the final qualitative narrative synthesis. This process was conducted to ensure comprehensive coverage of the literature while maintaining focus on clinically relevant evidence. Data were extracted and organized into predefined categories: periodontal parameters, oral microbiome composition changes, biofilm formation characteristics, and white spot lesions versus true caries incidence. Included papers were evaluated contextually according to their specific tier of evidence (e.g., separating direct clinical metrics from indirect in vitro or microbiological data). Formal meta-analytic quality scoring systems (e.g., Cochrane Risk of Bias tools) were not applied due to the narrative framework of this synthesis.

3. RESULTS

The included studies demonstrated notable variations in periodontal indices, microbial profiles, and demineralization risks between clear aligner therapy and conventional fixed orthodontic appliances. Most clinical investigations reported that removable aligner

systems were associated with more favorable short- and medium-term periodontal indices and reduced microbial dysbiosis during active treatment. In contrast, fixed appliances introduced complex, permanent plaque-retentive surfaces that promoted biofilm maturation and subsequent inflammatory changes.

3.1 Periodontal Health Outcomes (Clinical Evidence)

When distinguishing between different types of evidence, direct clinical trials demonstrate that patients treated with clear aligners, including systems such as Smartee, generally exhibit lower plaque indices, decreased gingival inflammation, and improved bleeding scores compared with patients undergoing fixed appliance therapy¹⁴.

Quantitative data from clinical studies demonstrate that patients treated with clear aligners show approximately 20–35% lower plaque index (PI) scores and 15–30% lower gingival index (GI) values compared with fixed appliance groups during the first 6–12 months of treatment. Several clinical trials also reported reduced bleeding on probing (BOP), with mean reductions ranging from 18% to 40% in aligner-treated patients. However, the long-term clinical significance of these differences remains modest, as long-term longitudinal studies show a narrowing gap between the two modalities as patients adapt over time. A comparative summary of periodontal outcomes is presented in Table 1.

Table 1. Comparison of periodontal outcomes between clear aligners and fixed appliances

Clinical Parameter	Clear Aligners	Fixed Appliances	Evidence Summary
Plaque Index (PI)	↓20–35%	Higher PI values	Multiple prospective studies
Gingival Index (GI)	↓15–30%	Higher GI values	Moderate evidence
Bleeding on Probing	Reduced	Increased	Consistent findings
Oral Hygiene Accessibility	Excellent	Limited	Strong consensus
White Spot Lesions	Lower prevalence	Higher prevalence (25–50%)	Clinical studies

3.2 Oral Microbiome and In Vitro Biofilm Changes (Microbiological & In Vitro Evidence)

Microbiological and in vitro studies provide a mechanistic look at the appliance environments. Fixed appliances are consistently linked to a higher pathogenic bacterial load, including Streptococcus mutans, Lactobacillus spp., Porphyromonas gingivalis, Prevotella intermedia, and Tannerella forsythia, showing significant

elevations within the first three months of therapy 8,16,20,28,29.

In contrast, clear aligner therapy demonstrates a more stable oral microbiome composition. While mild transient increases in cariogenic taxa such as *Streptococcus mutans* and *Actinomyces* spp. are occasionally observed in microbiological profiles during early treatment stages, these changes are less severe than those associated with fixed appliances and are heavily modulated by patient compliance and diet^{11,13,22,25}.

A detailed comparison of microbial changes is summarized in Table2.

Table 2. Microbiological differences between aligners and fixed appliances

Microbiological Outcome	Clear Aligners	Fixed Appliances	Clinical Significance
Streptococcus mutans	Mild transient increase	Significant increase	Higher caries risk in fixed appliances
Lactobacillus spp.	Stable	Increased	Associated with acidic biofilm
Microbial Diversity	Preserved	Reduced	Less dysbiosis with aligners
Periodontal Pathogens	Limited increase	Marked increase	Greater periodontal inflammation

The mechanism of biofilm development is summarized in Table 3 (embedded conceptual synthesis).

Table 3. Factors influencing biofilm formation on clear aligners

Risk Factor	Mechanism	Clinical Consequence	Prevention Strategy
Extended wear time (>20 h/day)	Reduced salivary clearance	Biofilm accumulation	Regular cleaning
Surface micro-abrasions	Increased bacterial adhesion	Mature biofilm formation	Timely aligner replacement
Salivary pellicle formation	Protein deposition	Microbial colonization	Mechanical cleaning
Poor hygiene compliance	Plaque retention	Caries and gingivitis risk	Patient education

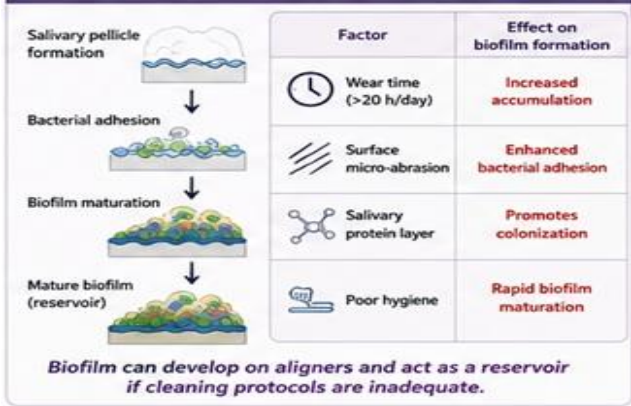


Figure 2. Factors influencing biofilm formation on clear aligners

3.3 White Spot Lesions vs. True Caries Incidence

A critical distinction must be made between enamel demineralization (white spot lesions) and true caries incidence. Clinical studies show that fixed appliances are more frequently associated with early enamel demineralization and white spot lesion formation around brackets, with a reported prevalence ranging from 25% to 50%^{17,21,23}.

Aligner-treated patients consistently demonstrate substantially lower rates of early white spot lesions due to the ability to remove the appliance for routine brushing and flossing^{17,21,23}.

However, true caries incidence between the two groups does not show as drastic a divergence. While aligners protect against general plaque accumulation, they can trap fermentable carbohydrates or sugary beverage residues against the enamel surface for 18–22 hours a day if patient compliance and dietary discipline are poor, potentially escalating a localized demineralization into true caries.

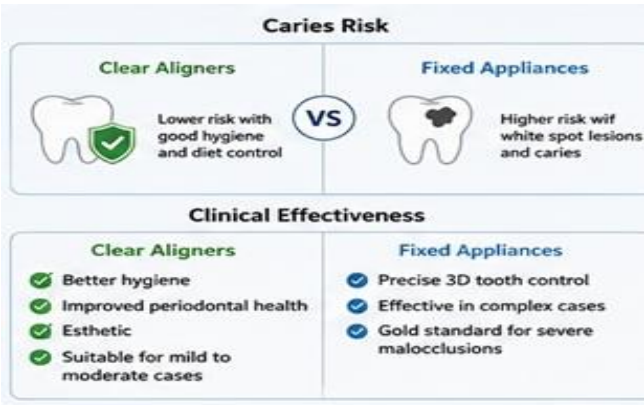


Figure 3. Comparison of Caries Risk and Enamel Demineralization of clear aligner therapy and fixed orthodontic appliances

The comparative analysis of the included studies revealed consistent differences between clear aligner therapy and conventional fixed orthodontic appliances with respect to periodontal health, microbial composition, oral hygiene accessibility, and enamel demineralization risk. Overall, clear aligners demonstrated a more favorable biological

profile, whereas fixed appliances were associated with greater plaque retention and microbial dysbiosis. A schematic overview of these key differences is presented in Figure 4.

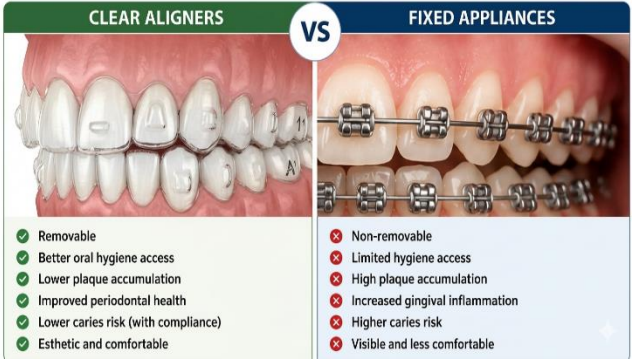


Figure 4. Schematic comparison of periodontal, microbiological, and oral hygiene-related characteristics associated with clear aligner therapy and fixed orthodontic appliances.

Table 4 summarizes the strength and consistency of the available evidence regarding the biological effects of clear aligner therapy, including periodontal outcomes, microbiological changes, and caries-related risks.

Table 4. Strength of evidence regarding the biological effects of clear aligner therapy

Outcome	Evidence Level	Consistency
Periodontal health	High	Strong
Plaque control	High	Strong
White spot lesion prevention	Moderate–High	Strong
Oral microbiome stability	Moderate	Moderate
Long-term caries reduction	Low–Moderate	Limited

DISCUSSION

The present narrative review evaluated the effects of clear aligner therapy on periodontal health, oral microbiome composition, and biofilm formation in comparison with fixed orthodontic appliances.

Overall, the available evidence indicates that aligner-based therapy may be associated with more favorable periodontal and oral hygiene outcomes; however, these differences appear modest and highly dependent on clinical conditions^{6,21,23,30}. A critical contribution of this review is highlighting that these biological and hygiene-related advantages are not automatic. While the removability of clear aligners facilitates mechanical plaque control, this advantage can be significantly compromised in daily clinical practice

18,21,23,31

Experimental findings suggest that such conditions may promote early biofilm formation on both teeth and aligner surfaces^{11,22,31,32}. From a clinical perspective, clear aligners offer advantages in periodontal health, aesthetics, and patient comfort. These benefits are closely linked to improved oral hygiene accessibility^{23,24,33}. Additionally, thermoplastic materials may undergo surface changes over time that increase microbial retention^{11,25,30}. Fixed appliances demonstrate a stronger and more consistent association with microbial dysbiosis, characterized by increased biofilm thickness, reduced microbial diversity, and elevated pathogenic bacterial load^{4,16,20,28,29}. These findings reinforce the role of appliance design in shaping the oral microbiome during orthodontic treatment.

Clinical studies consistently report higher levels of *Streptococcus mutans* and *Lactobacillus* species, increased gingival inflammation, and greater risk of white spot lesion formation in fixed appliance patients^{17,19,20,29}. Early deterioration of oral hygiene during fixed orthodontic therapy has also been documented, particularly in the initial months of treatment^{3,6,20,29}.

4.1 Practical Implications for Daily Aligner Practice

***Attachment-Rich Design & Auxiliaries:** The presence of numerous composite attachments, elastics, cutouts, or buttons changes the topography of the dentition. They create localized, fixed retentive niches similar to brackets, which can quickly reduce the inherent hygiene advantage of the aligner if not carefully cleaned^{21,23,30}.

*** Patient Compliance & Education:** Clear aligners are only "cleaner" if the patient follows a strict protocol. Without proper patient education regarding aligner cleaning, a disciplined diet (avoiding liquids other than water while wearing appliances), and compliance with the 22-hour wear rule, the aligner can transition from a protective shield to a closed biological reservoir for cariogenic shifts^{22,32}.

*** Individualized Risk Assessment:** Orthodontists should balance biological benefits with biomechanical requirements. Fixed systems remain the gold standard for severe rotational or complex skeletal corrections^{15,34,35}. However, for patients with pre-existing periodontal vulnerabilities or high initial demineralization risks, clear aligners represent an excellent therapeutic path—provided that an individualized risk profile is established at the start of treatment^{6,21,23}.

In this context, since clear aligner technology is rapidly evolving, dedicated research arms within major clinical pioneers, play a vital role^{11,34}. By facilitating collaborations with practicing orthodontists, generating large-scale clinical data, and exploring advanced material

sciences that resist surface microabrasions, such efforts help bridge the gap between indirect microbiological evidence and long-term clinical success.

Future research should focus on long-term longitudinal studies, standardized microbiome assessment protocols, and advanced sequencing methods to better understand microbial dynamics during orthodontic therapy^{16,20,25,31}.

5. CONCLUSIONS

Clear aligner therapy is associated with more favorable short- and medium-term periodontal and hygiene-related indices compared with fixed orthodontic appliances. However, these benefits are modest, conditional, and highly dependent on patient behavior, appliance design (such as the burden of attachments and auxiliaries), strict cleaning habits, and individualized risk assessment.

DECLARATIONS

Ethical Approval

Not applicable.

Competing Interests

The authors declare no conflict of interest.

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REVIEW ARTICLE

SALIVARY AND PERI-IMPLANT CREVICULAR FLUID BIOMARKERS IN PERI-IMPLANT DISEASES: A SCOPING REVIEW

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ABSTRACT

Background: Peri-implant diseases, including peri-implant mucositis and peri-implantitis, affect a substantial proportion of dental implant recipients and represent a major challenge for the long-term maintenance of implant-supported rehabilitation. Early identification of patients at risk of progression from reversible peri-implant mucositis to destructive peri-implantitis remains a significant clinical and diagnostic challenge.

Objective: To map the available evidence regarding biomarkers detected in saliva and peri-implant crevicular fluid (PICF) in peri-implant mucositis and peri-implantitis, and to identify molecular markers potentially associated with disease progression.

Materials and Methods: A scoping review was conducted according to PRISMA-ScR guidelines (2018). Electronic searches were performed in PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, and Google Scholar for studies published from 2000 - 2026. Eligible studies included human clinical investigations reporting quantitative analysis of biomarkers in saliva and/or peri-implant crevicular fluid (PICF) with appropriate comparison groups. In vitro studies, non-quantitative reports, and duplicate publications were excluded. A total of 31 studies met the inclusion criteria and were included in the final qualitative synthesis. Data were analyzed narratively, and biomarker patterns were summarized descriptively.

Results: The 31 included studies consistently reported elevated levels of pro-inflammatory and bone-resorption-related biomarkers in peri-implantitis. In peri-implant crevicular fluid, IL-1 β , TNF- α , IL-6, MMP-8, and RANKL, as well as an increased RANKL/OPG ratio, were the most frequently associated markers of disease activity. Transition from peri-implant mucositis to peri-implantitis was commonly associated with increased IL-17A, decreased IL-1 receptor antagonist (IL-1Ra), activation of matrix metalloproteinases, and markers of bone turnover such as CTX-I. Salivary biomarkers demonstrated lower diagnostic specificity compared to PICF; however, combined biomarker approaches, particularly IL-1 β and MMP-8 panels, showed moderate diagnostic performance for peri-implantitis detection.

Conclusion: Titanium remains the gold standard for dental implants because of its superior long-term survival, mechanical reliability, and extensive scientific validation. Zirconia implants represent a promising esthetic and metal-free alternative, particularly in anterior regions and selected clinical situations. Nevertheless, additional long-term studies are required to confirm their biomechanical reliability and long-term predictability.

Keywords: peri-implantitis, mucositis, biomarkers, saliva, PICF, cytokines, matrix metalloproteinases, RANKL, osteoprotegerin

INTRODUCTION

Dental implant therapy has become one of the most widely used treatment modalities for the rehabilitation of partial and complete edentulism. Continuous advances in implant design, biomaterials, surgical techniques, and prosthetic protocols have contributed to the high predictability and long-term success of implant-supported restorations. According to global market analyses and epidemiological reports, more than 15 million dental implants are placed annually worldwide, and the global dental implant market is projected to exceed USD 6.8 billion by 2028¹. Although dental implants demonstrate excellent long-term survival rates, with reported success rates ranging from 93% to 98% over five years of function², the maintenance of healthy peri-implant tissues remains a critical determinant of long-term treatment success.

Peri-implant diseases, including peri-implant mucositis and peri-implantitis, represent the most common biological complications associated with dental implants. These conditions are characterized by inflammatory reactions affecting the soft and hard tissues surrounding osseointegrated implants. According to the consensus report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions and the European Federation of Periodontology (EFP), peri-implant mucositis is defined as a reversible inflammatory lesion confined to the peri-implant mucosa without accompanying bone loss, whereas peri-implantitis is characterized by inflammation associated with progressive loss of supporting peri-implant bone³. Epidemiological studies indicate that peri-implant mucositis affects approximately 43–63% of implant patients, while peri-implantitis has been reported in 22–43% of individuals with functioning implants⁴. Considering the steadily increasing number of implant-supported restorations worldwide, these prevalence rates highlight the considerable clinical and public health burden associated with peri-implant diseases.

Despite substantial progress in implant dentistry, the timely identification of disease progression from reversible peri-implant mucositis to irreversible peri-implantitis remains a major clinical challenge. Current diagnostic protocols rely primarily on clinical and radiographic parameters, including probing depth (PD), bleeding on probing (BOP), suppuration, and radiographic assessment of marginal bone levels. While these parameters remain indispensable for routine clinical evaluation, they primarily reflect established tissue destruction rather than ongoing biological activity and therefore provide limited information regarding future disease progression.

One of the principal limitations of radiographic assessment is its inability to detect early pathological changes. Radiographically detectable bone loss generally becomes evident only after approximately 30–40% of the mineralized bone structure has been lost, indicating that substantial tissue destruction may occur before a definitive diagnosis is established⁵. Likewise, clinical signs such as increased probing depth and bleeding on probing frequently indicate the presence of existing inflammation rather than active molecular processes driving disease progression. Consequently, there is increasing interest in identifying biological markers capable of detecting pathological changes at an earlier stage, before clinically significant and irreversible tissue destruction becomes apparent.

The search for reliable biomarkers has emerged as an important area of research in contemporary implantology. Biomarkers present in oral fluids offer the possibility of identifying inflammatory and destructive processes at the molecular level before conventional clinical manifestations become evident. Among the biological matrices available for analysis, saliva and peri-implant crevicular fluid (PICF) have attracted particular attention because of their accessibility and their ability to reflect pathological processes occurring within peri-implant tissues.

PICF is a serum-derived inflammatory exudate collected from the peri-implant sulcus. Because it originates directly from the tissues surrounding the implant, its composition closely reflects local inflammatory activity, host immune responses, tissue degradation, and bone remodeling processes occurring at the implant site⁶. Saliva, in contrast, represents a readily obtainable and non-invasive biological fluid containing a broad spectrum of locally and systemically derived molecules, including cytokines, enzymes, degradation products, microbial metabolites, and oxidative stress markers^{7,8}. The ease and non-invasive nature of saliva collection make it particularly attractive for large-scale screening programs, longitudinal monitoring, and chairside diagnostic applications.

The pathogenesis of peri-implantitis involves a complex interaction between microbial biofilms and host immune-inflammatory responses. Current evidence indicates that disease progression is associated with dysregulation of inflammatory cytokine networks, activation of proteolytic enzymes, alterations in bone remodeling pathways, and increased oxidative stress^{9,10}. These biological mechanisms provide the rationale for investigating specific molecular markers that may serve as indicators of disease activity, tissue destruction, and progression risk.

Among inflammatory mediators, interleukin-1 β (IL-1 β) and tumor necrosis factor-alpha (TNF- α) are regarded as key initiators and amplifiers of the inflammatory cascade. Elevated levels of these cytokines promote leukocyte recruitment, stimulate osteoclastogenesis, and contribute to connective tissue destruction. Interleukin-17A (IL-17A), produced predominantly by T-helper 17 (Th17) lymphocytes, has emerged as a potential marker of advanced inflammatory activation and may play an important role in the transition from superficial mucosal inflammation to progressive bone destruction.

Matrix metalloproteinases (MMPs) constitute another important group of biomarkers involved in peri-implant tissue degradation. MMP-8, also known as neutrophil collagenase, is primarily responsible for degradation of collagen fibers within peri-implant soft tissues, whereas MMP-13 exhibits greater specificity for type I collagen degradation in mineralized tissues and may therefore be more directly associated with bone destruction. In addition, the receptor activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) signaling pathway represents a central regulatory mechanism governing osteoclast differentiation and bone resorption. An increased RANKL/OPG ratio reflects enhanced osteoclastic activity and has been consistently associated with peri-implant bone loss^{11,12}. Collectively, these biomarkers provide important insights into the molecular mechanisms underlying peri-implant disease progression and may contribute to the development of biologically driven diagnostic strategies.

Although numerous studies have investigated individual biomarkers in saliva and peri-implant crevicular fluid, the available evidence remains fragmented and heterogeneous. Furthermore, relatively few reviews have comprehensively examined biomarker dynamics across the entire spectrum of peri-implant disease, from peri-implant health through mucositis to established peri-implantitis, while simultaneously evaluating their potential role in identifying molecular events that may precede clinical and radiographic manifestations of disease progression.

Therefore, the aim of the present scoping review was to systematically map the available evidence regarding oral fluid biomarkers associated with peri-implant diseases. Specifically, this review sought to: (1) characterize cytokine, matrix metalloproteinase, and bone metabolism biomarker profiles in saliva and peri-implant crevicular fluid across different stages of peri-implant disease; (2) identify molecular markers potentially associated with the transition from peri-

implant mucositis to peri-implantitis; (3) compare the diagnostic and prognostic value of saliva and peri-implant crevicular fluid as biological sources of biomarkers; and (4) identify current knowledge gaps and priorities for future research aimed at advancing biomarker-based diagnosis and monitoring of peri-implant diseases.

2. MATERIALS AND METHODS

2.1. Study Design and Methodological Framework

This study was conducted as a scoping review following the methodological framework originally proposed by Arksey and O'Malley (2005) and subsequently refined by Levac et al. (2010). The review process was designed to systematically map the available evidence regarding oral fluid biomarkers associated with peri-implant diseases, identify research gaps, evaluate methodological heterogeneity, and summarize current knowledge concerning diagnostic and prognostic biomarkers in saliva and peri-implant crevicular fluid (PICF). This review was not prospectively registered in a publicly accessible database.

Reporting of the review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines published by Tricco et al. in 2018 [13]. In contrast to conventional systematic reviews, scoping reviews are intended to provide a comprehensive overview of the existing evidence base rather than perform a formal quantitative synthesis or risk-of-bias assessment. Consequently, no formal quality appraisal using instruments such as the Cochrane Risk of Bias Tool, Newcastle–Ottawa Scale, ROBINS-I, or GRADE framework was undertaken. This methodological approach was considered particularly appropriate because of the substantial heterogeneity among studies regarding patient populations, diagnostic definitions, biomarker panels, sample collection protocols, analytical platforms, and outcome reporting.

The review process followed five sequential stages: (1) identification of the research question; (2) systematic literature searching; (3) study selection according to predefined eligibility criteria; (4) structured data extraction and charting; and (5) synthesis and reporting of findings.

2.2. Eligibility Criteria

Inclusion Criteria

Studies were considered eligible when they met all of the following criteria:

1. Human clinical investigations, including randomized controlled trials (RCTs), prospective or retrospective cohort studies, cross-sectional studies, and case-control studies.
2. Quantitative evaluation of at least one biomarker related to inflammation, tissue degradation, bone metabolism, immune response, or oxidative stress in saliva and/or peri-implant crevicular fluid.
3. Presence of a clearly defined comparison group, including peri-implant health, peri-implant mucositis, peri-implantitis, or healthy periodontal controls.
4. Use of standardized biological sampling procedures, including collection of PICF using absorbent paper strips (PerioPaper®, PerioScan®, or equivalent methods), microcapillary sampling, or direct fluid collection, and collection of unstimulated or stimulated whole saliva according to established protocols.
5. Availability of full-text articles.

The time restriction was selected to ensure inclusion of studies conducted using contemporary molecular analytical techniques and diagnostic concepts that are compatible with the 2017 World Workshop classification of periodontal and peri-implant diseases.

Exclusion Criteria

Studies were excluded when one or more of the following criteria were present:

1. Experimental studies conducted exclusively in vitro or in animal models without validation through human clinical investigations.
2. Studies reporting only qualitative findings without quantitative biomarker measurements.
3. Absence of a clear clinical distinction between peri-implant mucositis and peri-implantitis.
4. Sample size smaller than 10 participants.
5. Duplicate publications, secondary analyses, or multiple reports derived from the same patient cohort, in which case the most complete and informative publication was retained.

6. Studies using dental implants solely as experimental models for periodontitis research without specific evaluation of peri-implant tissues.

2.3. Information Sources and Search Strategy

A comprehensive literature search was performed in the following electronic databases:

- PubMed/MEDLINE
- Scopus
- Web of Science Core Collection
- Cochrane Library
- Google Scholar

The search covered publications from 2000-2026.

In addition to electronic database searching, manual screening of reference lists from all included studies and relevant review articles was performed (backward citation searching). To minimize publication bias and identify potentially relevant unpublished studies, gray literature searches were conducted through Open Grey and the International Prospective Register of Systematic Reviews (PROSPERO).

The search strategy was developed using a combination of controlled vocabulary terms and free-text keywords related to peri-implant diseases, biomarkers, inflammatory mediators, and oral fluids. The complete PubMed/MEDLINE search syntax was as follows:

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((("peri-implantitis"[Title/Abstract] OR "peri-implant disease"[Title/Abstract] OR "peri-implant mucositis"[Title/Abstract] OR "periimplant inflammation"[Title/Abstract])) AND ("biomarker*" [Title/Abstract] OR "cytokine*" [Title/Abstract] OR "interleukin*" [Title/Abstract] OR "IL-1*" [Title/Abstract] OR "TNF-alpha" [Title/Abstract] OR "matrix metalloproteinase*" [Title/Abstract] OR "MMP*" [Title/Abstract] OR "RANKL" [Title/Abstract] OR "OPG" [Title/Abstract] OR "osteoprotegerin" [Title/Abstract])) AND ((saliva [Title/Abstract] OR "peri-implant crevicular fluid" [Title/Abstract] OR PICF [Title/Abstract] OR "oral fluid*" [Title/Abstract]))
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Equivalent search strategies adapted to the indexing systems and syntax requirements of each database were subsequently applied. No language restrictions were imposed during the search process.

2.4. Study Selection Process

All records retrieved from database searches were imported into the Rayyan QCRI systematic review platform to facilitate duplicate removal, screening, and study management.

Study selection was conducted independently by two reviewers (Researcher 1 and Researcher 2) in two consecutive stages. In the first stage, titles and abstracts were screened for potential eligibility. In the second stage, full-text articles were assessed against predefined inclusion and exclusion criteria. Any disagreements between reviewers were resolved through discussion and consensus. When consensus could not be reached, a third reviewer (Researcher 3) acted as an arbitrator.

Inter-reviewer agreement during full-text assessment was evaluated using Cohen's kappa coefficient (κ), demonstrating excellent agreement ($\kappa = 0.84$; 95% CI: 0.76–0.92) according to the Landis and Koch classification.

The study selection process followed PRISMA-ScR recommendations. A total of 1,847 records were identified through electronic database searching. After removal of 435 duplicate records, 1,412 unique publications remained for title and abstract screening. Of these, 1,198 records were excluded as not relevant to the review objectives.

Subsequently, 214 full-text articles were retrieved and assessed for eligibility. Following full-text evaluation, 183 articles were excluded for the following reasons:

- Lack of quantitative biomarker analysis ($n = 74$)
- In vitro or animal studies only ($n = 45$)
- Insufficient sample size (<10 participants) ($n = 32$)
- Lack of clear distinction between peri-implant mucositis and peri-implantitis ($n = 23$)
- Duplicate publications or secondary analyses ($n = 9$)

Ultimately, **31 studies** met all eligibility criteria and were included in the final qualitative and narrative synthesis (Figure 1).

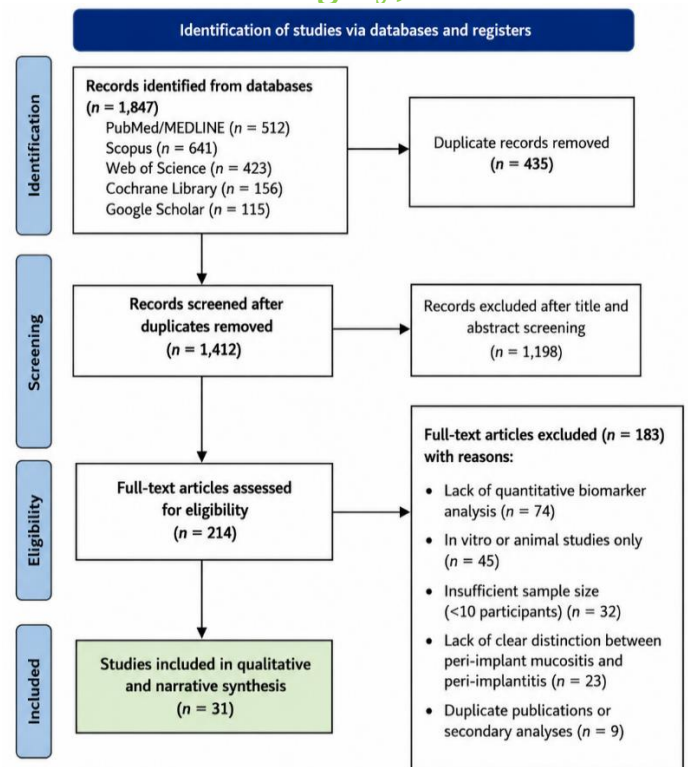


Figure 1. PRISMA flow diagram of study selection process.

2.5. Data Extraction and Charting

Data extraction was performed using a standardized electronic spreadsheet developed specifically for this review. Two investigators independently extracted data, and discrepancies were resolved through discussion and verification of the original publications.

The following categories of information were collected from each included study:

Bibliographic Characteristics

- First author
- Year of publication
- Country of origin
- Journal title
- Journal Citation Reports (JCR) impact factor

Methodological Characteristics

- Study design (cross-sectional, case-control, cohort study, or randomized controlled trial)
- Total sample size
- Distribution of participants among study groups
- Participant inclusion and exclusion criteria
- Duration of follow-up and observation period

Clinical Characteristics

- Diagnostic criteria used for peri-implant mucositis and peri-implantitis
- Probing depth (PD)
- Bleeding on probing (BOP)
- Radiographic bone loss (RBL)
- Implant-related characteristics, including implant design, surface characteristics, and functional loading duration

Biomaterial Collection and Laboratory Analysis

- Type of biological specimen analyzed (PICF, saliva, or both)
- Sample collection procedures
- Timing and conditions of sample collection
- Storage and processing protocols when reported
- Analytical platform utilized, including enzyme-linked immunosorbent assay (ELISA), Luminex multiplex analysis, reverse transcription quantitative polymerase chain reaction (RT-qPCR), liquid chromatography–tandem mass spectrometry (LC-MS/MS), or other validated methods

Biomarker and Statistical Outcomes

- Biomarkers investigated
- Absolute biomarker concentrations or enzymatic activity values
- Measures of central tendency and dispersion (mean $\pm$ standard deviation or median with interquartile range)
- Statistical tests employed
- Reported p-values
- Correlation coefficients with clinical parameters
- Receiver operating characteristic (ROC) analyses and area under the curve (AUC) values when available
- Diagnostic sensitivity, specificity, and predictive performance metrics

2.6. Data Synthesis

Because substantial methodological heterogeneity was identified among the included studies, a quantitative meta-analysis was not considered appropriate. Sources of heterogeneity included variations in study design, patient populations, diagnostic criteria, biomaterial collection procedures, laboratory processing protocols, analytical platforms, calibration standards, units of measurement, antibody specificity, polymerase chain

reaction primers, and statistical reporting methods.

Consequently, data synthesis was performed using a narrative approach. Studies were grouped according to the biological matrix analyzed (peri-implant crevicular fluid, saliva, or combined analysis) and subsequently categorized by biomarker class, including inflammatory cytokines, matrix metalloproteinases, bone metabolism markers, immune mediators, and oxidative stress markers.

Descriptive statistical methods were used to summarize and compare biomarker concentrations across peri-implant health, peri-implant mucositis, and peri-implantitis groups. Where appropriate, median values, concentration ranges, fold changes, and interquartile distributions reported in the original studies were compared. The results were synthesized in structured summary tables organized according to biomarker category and biological specimen type.

Particular emphasis was placed on identifying biomarkers consistently associated with peri-implant disease severity, biomarkers potentially involved in the transition from peri-implant mucositis to peri-implantitis, and biomarkers demonstrating diagnostic or prognostic utility across multiple independent studies. In addition, methodological trends, areas of consensus, sources of variability, and current knowledge gaps were evaluated to identify priorities for future research and facilitate the development of standardized biomarker-based diagnostic protocols.

2.7. Ethical Considerations

This scoping review was based exclusively on the analysis and synthesis of previously published scientific literature. No human participants were recruited, no biological samples were collected, and no patient-identifiable information was accessed by the authors during the conduct of this review.

All studies included in the review were required to report compliance with relevant ethical standards and, where applicable, approval by institutional ethics committees or review boards and the acquisition of informed consent from participants in accordance with the Declaration of Helsinki and local regulatory requirements. Because the present investigation involved only secondary analysis of published data, separate ethical approval and informed consent were not required for this review.

3. RESULTS

3.1. Characteristics of the Included Studies

A total of **31 studies** published between 2010 and 2024 met the eligibility criteria and were included in the final qualitative synthesis. Collectively, these studies involved 2,186 participants diagnosed with peri-implant health, peri-implant mucositis, peri-implantitis, or healthy peri-implant/periodontal conditions used as comparator groups. The mean sample size across studies was approximately 62 participants, with individual study populations ranging from 10 to 180 subjects

The methodological characteristics of the included studies demonstrated substantial diversity. Cross-sectional investigations represented the most common study design, accounting for 17 studies (54.8%). Nine studies (29.0%) employed a case-control design, while four studies (12.9%) were conducted as prospective cohort investigations. Only one study (3.2%) was a randomized controlled clinical trial. The predominance of observational study designs reflects the exploratory nature of biomarker research in peri-implant diseases.

Regarding biological specimen collection, peri-implant crevicular fluid (PICF) was the most frequently investigated diagnostic medium. Twenty studies (64.5%) analyzed biomarkers exclusively in PICF, reflecting its close association with local peri-implant tissue conditions. Saliva was evaluated as the sole biological matrix in seven studies (22.6%), whereas four studies (12.9%) simultaneously assessed biomarkers in both PICF and saliva, enabling comparative analysis between local and whole-mouth biomarker profiles.

Considerable variation was also observed in laboratory methodologies. Enzyme-linked immunosorbent assay (ELISA) was the predominant analytical technique and was utilized in 23 studies (74.2%). Multiplex immunoassay platforms (Luminex/Bio-Plex) were employed in four studies (12.9%). Real-time quantitative PCR (RT-qPCR) was used in two studies (6.5%), while two studies (6.5%) applied mass spectrometry-based proteomic approaches. This methodological heterogeneity contributed to variability in reported biomarker concentrations and limited direct quantitative comparison across studies.

The included studies were conducted across 19 countries, reflecting broad international interest in biomarker-based diagnostics for peri-implant diseases.

The highest concentration of publications originated from Sweden, Switzerland, Brazil, Germany, and the United States, which together accounted for the majority of included studies.

Overall, the included literature represents a heterogeneous but methodologically informative body of evidence encompassing diverse populations, biomarker panels, and analytical approaches. This diversity provides a comprehensive overview of current knowledge while highlighting the need for greater methodological standardization in future research.

Table 1. Characteristics of the included studies according to biomaterial type and study design

Type of biomaterial	Cross-sectional	Case-control	Cohort	RCT	Total
PICF	11 (55.0%)	6 (30.0%)	3 (15.0%)	0(0%)	20
Saliva	4 (57.1%)	2 (28.6%)	1 (14.3%)	0 (0%)	7
PICF + Saliva	2 (50.0%)	1 (25.0%)	1 (25.0%)	0 (0%)	4
Total	17 (54.8%)	9 (29.0%)	4 (12.9%)	1(3.2 %)	31

3.2. Cytokine Profiles in Peri-Implant Crevicular Fluid (PICF)

Interleukin-1 beta (IL-1 β)

Interleukin-1 β (IL-1 β) was the most frequently investigated proinflammatory cytokine across the included studies (n = 28). Consistently elevated concentrations were observed in peri-implantitis compared with peri-implant mucositis and healthy implant conditions.

Reported PICF concentrations ranged as follows:

- Peri-implantitis: 80–160 pg/mL
- Peri-implant mucositis: 25–45 pg/mL
- Healthy implants: 8–15 pg/mL

Overall, IL-1 β levels were increased approximately 6.5–12.4-fold in peri-implantitis compared with healthy peri-implant sites. Diagnostic performance analysis from included studies demonstrated an area under the ROC curve (AUC) ranging from 0.84 to 0.91, indicating good discriminatory ability.

A previously reported threshold increase of IL-1 β $\geq$ 50 pg/mL has been associated with inflammatory peri-implant conditions, demonstrating a sensitivity of 81.3% and specificity of 76.8% in periodontal settings; however, peri-implant-specific cut-off values remain insufficiently standardized due to variability in sampling techniques and fluid volume [14]. IL-1 β levels demonstrated significant correlations with clinical and radiographic parameters, including probing depth ($r = 0.63\text{--}0.74$; $p < 0.001$) and radiographic bone loss ($r = 0.58\text{--}0.69$; $p < 0.001$), supporting its role as both a diagnostic and disease severity-associated biomarker.

Tumor Necrosis Factor-alpha (TNF- α)

TNF- α concentrations in PICF were consistently elevated in peri-implantitis, showing an increase of approximately 2.4–5.1-fold compared with healthy conditions. Reported values ranged from 35–65 pg/mL in peri-implantitis versus 5–12 pg/mL in healthy sites.

Evidence from 12 studies indicated that TNF- α may be associated with disease progression. In limited prospective cohort data, elevated TNF- α levels were reported prior to radiographic evidence of bone loss, suggesting a potential role as an early indicator of disease progression¹⁵. However, further longitudinal validation is required.

Interleukin-6 (IL-6) and Interleukin-8 (IL-8)

IL-6 levels were significantly increased in peri-implantitis (35–72 pg/mL) compared with healthy implants (4–10 pg/mL), representing a 3.1–6.8-fold elevation. IL-6 demonstrated moderate to strong correlations with matrix metalloproteinase-8 (MMP-8) levels ($r = 0.51\text{--}0.67$), suggesting coordinated activation of inflammatory and proteolytic pathways¹⁶.

IL-8 (CXCL8), a key neutrophil chemokine, was also elevated in peri-implant diseases; however, its diagnostic specificity was lower than that of IL-1 β . Reported sensitivity ranged from 62–70%, with specificity between 60–68%. IL-8 demonstrated limited ability to differentiate peri-implant mucositis from peri-implantitis, indicating restricted clinical utility as a standalone biomarker.

Interleukin-17A (IL-17A) and Anti-inflammatory Mediators

IL-17A demonstrated a distinct expression pattern associated with disease progression. Its levels were significantly elevated in peri-implantitis (18–42

pg/mL), while remaining low in peri-implant mucositis (5–10 pg/mL) and healthy conditions (<5 pg/mL) ($p < 0.001$). The observed increase of approximately 4.5–10-fold suggests a strong association with transition from reversible to irreversible disease stages.

These findings indicate that IL-17A may reflect activation of Th17-mediated immune pathways and may represent a potential marker of disease progression rather than early inflammatory initiation.

IL-1 receptor antagonist (IL-1Ra) is consistently reduced in peri-implantitis, indicating impaired local anti-inflammatory regulation. The IL-1 β /IL-1Ra ratio in peri-implantitis is 0.43 ± 0.18 versus 0.12 ± 0.06 in mucositis ($p < 0.001$), reflecting a pathological imbalance of pro-inflammatory and anti-inflammatory signals.

3.3. Matrix Metalloproteinases and Markers of Extracellular Matrix Degradation

Matrix Metalloproteinase-8 (MMP-8, Neutrophil Collagenase)

Matrix metalloproteinase-8 (MMP-8) was the most extensively investigated proteolytic enzyme across the included studies and represents a key biomarker of extracellular matrix degradation in peri-implant diseases. Based on 16 studies, MMP-8 concentrations in peri-implant crevicular fluid (PICF) showed a marked increase in peri-implantitis compared with mucositis and healthy implants.

Reported concentrations ranged from:

- Peri-implantitis: 112–187 ng/mL
- Peri-implant mucositis: 34–56 ng/mL
- Healthy implants: 20–40 ng/mL

Overall, MMP-8 levels were increased by approximately 3.5–7.2-fold in peri-implantitis compared with healthy conditions ($p < 0.001$). MMP-8 demonstrated a strong positive correlation with radiographic bone loss ($r = 0.65\text{--}0.71$; $p < 0.001$), supporting its role as both an inflammatory and tissue-destructive biomarker. Diagnostic performance was consistently high, with reported area under the ROC curve (AUC) values ranging from 0.80 to 0.88.

Matrix Metalloproteinase-13 (MMP-13, Collagenase-3)

MMP-13, primarily expressed by osteoblasts and

osteoclast-associated cells, is considered a marker more specifically associated with bone tissue degradation. In PICEF, MMP-13 levels were significantly elevated in peri-implantitis (10–28 ng/mL) compared with mucositis (2–5 ng/mL; $p < 0.01$), corresponding to an approximate 5.0–14-fold increase.

MMP-13 demonstrated a significant correlation with radiographic bone loss ($r = 0.60\text{--}0.72$; $p < 0.001$), indicating its relevance to active bone remodeling and destruction. These findings suggest that MMP-13 may serve as a more specific indicator of the transition from soft tissue inflammation to hard tissue breakdown.

Other Matrix Metalloproteinases and Tissue Degradation Markers

MMP-9 (gelatinase B), primarily derived from neutrophils and macrophages, reflects general inflammatory activity within peri-implant tissues. Its levels increase in association with disease severity and probing depth; however, its diagnostic accuracy is lower compared with MMP-8 (AUC: 0.70–0.78).

Aspartate aminotransferase (AST) activity in PICEF has also been proposed as a marker of cellular damage and tissue necrosis. Across five studies, AST activity was significantly higher in peri-implantitis compared with mucositis (mean: 43.8 IU/L vs. 18.2 IU/L; $p < 0.05$), supporting its potential role as a non-specific indicator of tissue breakdown.

3.4. Bone Metabolism Markers: The RANKL/OPG Axis and Collagen Degradation Products

RANKL–RANK–OPG Signaling System

The receptor activator of nuclear factor kappa-B ligand (RANKL)–receptor activator of nuclear factor kappa-B (RANK)–osteoprotegerin (OPG) axis represents a central regulatory pathway in osteoclast differentiation and bone resorption, and is of fundamental importance in peri-implantitis pathophysiology.

Based on 11 studies, RANKL concentrations in PICEF were significantly elevated in peri-implantitis compared with mucositis and healthy implants:

- Peri-implantitis: 28–55 pg/mL
- Peri-implant mucositis: 8–18 pg/mL
- Healthy implants: 2–5 pg/mL

This corresponds to an approximate 7.1–11.3-fold increase in peri-implantitis ($p < 0.001$). In contrast,

OPG levels were reduced in peri-implantitis (30–60 pg/mL) compared with healthy implants (80–130 pg/mL), representing a 2–3-fold decrease ($p < 0.001$). These findings reflect a shift toward a pro-resorptive microenvironment favoring osteoclast activation.

RANKL/OPG Ratio

The RANKL/OPG ratio emerged as one of the most robust indicators of peri-implant bone resorption activity. Reported values were:

- Peri-implantitis: 2.1–3.8
- Mucositis: 0.6–0.9
- Healthy implants: 0.2–0.4

The ratio was increased approximately 10-fold in peri-implantitis compared with healthy conditions ($p < 0.001$). Diagnostic performance was excellent, with reported AUC values ranging from 0.87 to 0.93.

In limited longitudinal studies, elevated RANKL/OPG ratios were associated with subsequent radiographic bone loss, suggesting potential utility as a predictive marker of disease progression^{18,19}.

Osteocalcin and Osteopontin

Osteocalcin, a marker of osteoblastic activity and bone formation, was consistently reduced in PICEF during active peri-implantitis, reflecting suppression of bone formation processes in favor of resorption-dominated remodeling.

Osteopontin (SPP1), in contrast, was elevated in peri-implantitis and demonstrated a positive correlation with inflammatory severity ($r = 0.61$; $p < 0.01$). This supports its role as a marker associated with osteoclast activation and bone resorption activity.

Collagen Type I C-terminal Telopeptide (CTX-I)

CTX-I, a specific degradation product of type I collagen, represents a direct marker of osteoclastic bone resorption. In PICEF, CTX-I levels were significantly increased in active peri-implantitis (4–12 ng/mL) compared with stable peri-implantitis (1–2.5 ng/mL) and mucositis (<1 ng/mL; $p < 0.001$).

These findings indicate that CTX-I may be particularly useful for monitoring disease activity and evaluating treatment response in peri-implant inflammatory conditions

Table 2. Key PICF biomarkers: concentrations and diagnostic value

Biomarker	Norm	Mucositis	Peri-implantitis	Frequency ↑	Relationship with bone loss
IL-1 β	8-15 pg/ml	25-45	80-160 pg/ml	6,5-12,4×	r = 0,58-0,69
TNF- α	5-12 pg/ml	16-28	35-65 pg/ml	2,4-5,1×	r = 0,48-0,62
IL-6	4-10 pg/ml	15-25	35-72 pg/ml	3,1-6,8×	r = 0,51-0,64
IL-8	25-50 pg/ml	70-120	140-280 pg/ml	2,8-5,6×	r = 0,39-0,55
IL-17A	< 5 pg/ml	5-10	18-42 pg/ml	4,5-10,0×	r = 0,55-0,67
MMP-8	20-40 ng/ml	35-56	112-187 ng/ml	3,5-7,2×	r = 0,65-0,71
MMP-13	< 2 ng/ml	2-5	10-28 ng/ml	5,0-14×	r = 0,60-0,72
RANKL	2-5 pg/ml	8-18	28-55 pg/ml	7,1-11,3×	r = 0,67-0,78
OPG	80-130 pg/ml	65-100	30-60 pg/ml	↓ 2-3×	r = -0,55 - -0,68
RANKL/OPG	0,2-0,4	0,6-0,9	2,1-3,8	≈ 10×	r = 0,72-0,81
CTX-I	< 1 ng/ml	1-2,5	4-12 ng/ml	4,5-12×	r = 0,63-0,74

Note: M - mean values; SD - standard deviation; Me - median; IQR - interquartile range; CI - confidence interval; AUC - area under the ROC curve.

3.5. Salivary Biomarkers in Peri-Implant Diseases

Saliva represents an alternative and clinically attractive biological matrix for the assessment of peri-implant diseases due to its non-invasive collection, cost-effectiveness, and suitability for repeated longitudinal monitoring. These characteristics make saliva particularly valuable for large-scale screening and population-based diagnostic approaches. However, compared with peri-implant crevicular fluid (PICF), saliva is a less site-specific diagnostic fluid, as it reflects a mixture of secretions originating from major and minor salivary glands, gingival crevicular fluid, and other oral and systemic sources. This dilution effect reduces its specificity for localized peri-implant inflammatory processes.

Cytokines and Proteolytic Enzymes in Saliva

Salivary interleukin-1 β (IL-1 β) is consistently elevated in peri-implantitis, showing approximately a 2.3–4.1-fold increase compared with healthy conditions (healthy range: 5–8 pg/mL; peri-implantitis: 15–30 pg/mL). Salivary IL-1 β levels demonstrate a moderate-to-strong correlation with PICF concentrations (r = 0.58–0.72), suggesting that salivary cytokine levels partly reflect local peri-implant inflammatory activity. However, diagnostic specificity remains limited due to contributions from other oral inflammatory sources and systemic influences.

Matrix metalloproteinase-8 (MMP-8) is one of the most consistently elevated salivary biomarkers in peri-implantitis. Reported median concentrations are significantly higher in peri-implantitis (68.4 ng/mL) compared with peri-implant mucositis (28.7 ng/mL; p < 0.01). The clinical applicability of salivary MMP-8 has been strengthened by commercially available point-of-care diagnostic systems such as PerioSafe® and OraLyzer®, which have demonstrated diagnostic potential in implant patients across several clinical studies²⁰.

Matrix metalloproteinase-9 (MMP-9) is also elevated in peri-implant disease; however, its diagnostic performance is limited by high biological variability and lower specificity compared with MMP-8. Neutrophil elastase (NE), another marker of neutrophil activation, is increased in peri-implantitis and correlates with the severity of clinical inflammation, reflecting active innate immune response within the oral cavity ²¹.

Oxidative Stress-Related Biomarkers in Saliva

Salivary oxidative stress markers demonstrate a characteristic imbalance in peri-implant diseases. Uric acid levels are reduced in peri-implantitis, reflecting its consumption as part of antioxidant defense mechanisms. In contrast, malondialdehyde (MDA), a marker of lipid peroxidation, is significantly elevated, indicating increased oxidative damage to cellular membranes ²².

Similarly, 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, is significantly increased in patients with peri-implantitis compared with individuals with healthy implants ($p < 0.05$). These findings collectively indicate enhanced reactive oxygen species (ROS) production and systemic oxidative imbalance associated with peri-implant inflammatory processes.

Bone Metabolism Markers and Acute Phase Proteins in Saliva

Salivary osteopontin is elevated in peri-implantitis and has been shown to correlate positively with clinical parameters of disease severity. In the study by Lee et al. (2023), osteopontin levels demonstrated a significant correlation with probing depth around implants ($r = 0.59$; $p < 0.01$), suggesting its involvement in active inflammatory bone remodeling processes.

Lactoferrin, a neutrophil-derived antimicrobial glycoprotein, is also increased in saliva in peri-implantitis. Its elevation reflects sustained neutrophil activation and prolonged inflammatory activity within the oral environment, further supporting its role as a marker of chronic peri-implant inflammation ²³.

Overall, while salivary biomarkers demonstrate consistent trends reflecting peri-implant inflammatory activity, their diagnostic specificity remains lower than that of PICF-based biomarkers. Nevertheless, salivary multi-marker panels, particularly those combining inflammatory and proteolytic markers, may provide valuable non-invasive tools for screening and monitoring peri-implant disease progression.

Salivary biomarkers show a progressive increase from peri-implant mucositis to peri-implantitis, with IL-1 β and MMP-8 demonstrating the highest diagnostic accuracy and combined biomarker panels providing superior performance (Table 3).

Table 3. Salivary biomarkers in peri-implant diseases and their diagnostic performance

Biomarker	Peri-implant mucositis	Peri-implantitis	Diagnostic value	Sensitivity / Specificity (%)
IL-1 β	Mild increase (↑)	Moderate–marked increase (↑↑)	Moderate	71-78 / 65-72
MMP-8	Mild increase (↑)	Marked increase (↑↑)	Moderate	68-75 / 67-74

Biomarker	Peri-implant mucositis	Peri-implantitis	Diagnostic value	Sensitivity / Specificity (%)
MMP-9	Minimal increase (↑)	Moderate increase (↑)	low	54-62 / 58-65
IL-6	Minimal increase (↑)	Moderate increase (↑)	Moderate	62-70/ 60-68
Neutrophil elastase	Mild increase (↑)	Marked increase (↑↑)	Moderate	65-72 / 63-70
Osteopontin	Minimal increase (↑)	Moderate increase (↑)	Moderate	60-67/ 58-66
Malondialdehyde (MDA)	Minimal increase (↑)	Moderate increase (↑)	low	55-63/ 52-60
IL-1 β + MMP-8 combination	-	Marked increase (↑↑)	Good (highest performance)	73-78/ 70-76
Lactoferrin	Minimal increase (↑)	Moderate increase (↑)	low	52-60/ 50-58

3.6. Comparative Analysis of the Diagnostic Value of PICF and Saliva

A direct comparison between peri-implant crevicular fluid (PICF) and saliva was reported in 8 studies included in this review. Across all comparative investigations, PICF consistently demonstrated superior diagnostic performance in distinguishing peri-implant health, mucositis, and peri-implantitis when compared with salivary biomarkers.

For interleukin-1 β (IL-1 β), the area under the receiver operating characteristic curve (AUC) in PICF ranged from 0.84 to 0.91, whereas salivary IL-1 β demonstrated lower diagnostic accuracy, with AUC values ranging from 0.67 to 0.76 ²⁴. These findings confirm the higher site-specific diagnostic value of PICF in peri-implant inflammatory conditions.

Nevertheless, several studies highlighted that saliva retains independent diagnostic potential when analyzed using standardized collection protocols and multi-marker approaches. In particular, a salivary biomarker panel comprising IL-1 β , MMP-8, IL-6, and osteopontin demonstrated an AUC of 0.82 for the diagnosis of peri-implantitis in the study by Sánchez-Jiménez et al. (2023), indicating performance comparable to single-marker PICF-based assays ²⁵.

The diagnostic advantage of PICF was most pronounced for markers directly associated with bone remodeling and resorption, including RANKL, OPG, and CTX-I, which were either absent or present at significantly lower and less reliable concentrations in saliva. In contrast, saliva provided a broader representation of the systemic and generalized inflammatory response, as well as oxidative stress and antioxidant status, reflecting its mixed biological origin.

Overall, PICF demonstrates higher specificity for local peri-implant tissue destruction, whereas saliva offers advantages for non-invasive screening and systemic inflammatory profiling. Therefore, the two biological fluids should be considered complementary rather than competing diagnostic matrices.

3.7. Molecular Markers of the Transition from Mucositis to Peri-Implantitis

The identification of molecular events associated with the transition from reversible peri-implant mucositis to irreversible peri-implantitis represents a central objective of this review. Based on data from 11 prospective and longitudinal studies, a stepwise molecular progression model can be proposed.

Stage 1: Early Peri-Implant Mucositis (Reversible Phase)

In the early inflammatory phase, the molecular profile is dominated by early pro-inflammatory cytokines, primarily interleukin-1 β (IL-1 β) and tumor necrosis factor-alpha (TNF- α), produced mainly by activated macrophages and innate immune cells in response to microbial biofilm accumulation. At this stage, bone metabolism remains largely balanced, and the RANKL/OPG ratio remains below 1.0, indicating predominance of osteoprotective signaling.

Matrix metalloproteinase-8 (MMP-8) is moderately elevated, reflecting early extracellular matrix degradation confined to peri-implant soft tissues without evidence of bone involvement. This phase remains clinically reversible with effective plaque control and inflammation management.

Transition Phase: Molecular Switch to Peri-Implantitis

The transition to peri-implantitis is associated with activation of the IL-17A-mediated Th17 immune pathway. Differentiation of naïve T cells into Th17 cells leads to increased expression of RANKL by osteoblasts and stromal cells, resulting in a shift in bone metabolism toward osteoclastogenesis. At this point, the RANKL/OPG ratio exceeds 1.0, marking a critical threshold for net bone resorption.

Concurrently, MMP-13 becomes detectable in peri-implant crevicular fluid, indicating active degradation of type I bone collagen. A reduction in interleukin-1 receptor antagonist (IL-1Ra) is also observed, reflecting depletion of endogenous anti-inflammatory regulatory mechanisms. These combined changes suggest the initiation of irreversible bone tissue damage, which may precede radiographic detection.

Stage 2: Advanced Peri-Implantitis (Irreversible Phase)

Advanced peri-implantitis is characterized by a pronounced and sustained upregulation of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6, and IL-8), extensive activation of matrix metalloproteinases (particularly MMP-8 and MMP-13), and a persistently elevated RANKL/OPG ratio (typically $\gg$ 2.0), indicating dominant osteoclastogenic activity.

The appearance of collagen degradation products such as C-terminal telopeptide of type I collagen (CTX-I), together with decreased osteocalcin levels, confirms active bone resorption and suppression of osteoblastic activity. At this stage, structural bone loss becomes radiographically evident and is generally considered irreversible, often requiring surgical and regenerative therapeutic approaches.

Table 4 summarizes the stepwise molecular changes of PICF biomarkers during peri-implant disease

progression, showing a transition from early cytokine-driven inflammation in mucositis to pronounced activation of proteolytic enzymes and dysregulated bone resorption pathways in peri-implantitis. Overall, the biomarker profile demonstrates a consistent shift toward a pro-inflammatory and pro-osteoclastic environment as disease severity increases.

Table 4. Molecular dynamics of PICF biomarkers during peri-implant disease progression

Biomarker	Healthy implant	Mucositis	Early peri- implantitis	Advanced peri- implantitis
IL-1 β	—	+	++	+++
TNF- α	—	+	++	++
IL-6	—	+	++	+++
IL-17A	—	–/+	++	+++
IL-1Ra	+++	++	+	–/+
MMP-8	—	+	++	+++
MMP-13	—	—	+	+++
RANKL	—	+	++	+++
OPG	+++	++	+	–/+
RANKL/OPG	↓↓ (0,2-0,4)	↓ (0,6-0,9)	↑ (1,0-1,5)	↑↑↑ (2,1-3,8)
CTX-I	—	—	+	+++
Osteocalcin	++	++	+	—

Note: "—" - not determined/normal; "+" - slight increase; "++" - moderate increase; "+++" - marked increase; "↓↓" - marked decrease; "↑↑↑" - marked increase in the ratio.

4.1. Interpretation of Results in the Context of the Pathophysiology of Peri-Implantitis

The findings of this scoping review support a stepwise molecular model of peri-implant disease progression that shares similarities with, yet is mechanistically distinct from, classical periodontitis. In the initial phase, microbial biofilm formation on implant surfaces—predominantly composed of Gram-negative anaerobic species such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*—activates the innate immune system through pattern recognition receptors (PRRs) expressed on macrophages and dendritic cells. This interaction induces moderate secretion of pro-inflammatory cytokines, primarily IL-1 β and TNF- α , by neutrophils and macrophages. Under physiological conditions, local regulatory mediators, including IL-1 receptor antagonist (IL-1Ra), osteoprotegerin (OPG), and transforming growth factor- β (TGF- β), maintain inflammatory homeostasis, thereby confining the process to reversible peri-implant mucositis²⁶.

With persistent biofilm accumulation and chronic antigenic stimulation, a progressive breakdown of local immunoregulatory mechanisms occurs. This stage is characterized by a reduction in IL-1Ra, resulting in an imbalance between pro- and anti-inflammatory signaling pathways. Concurrently, T-helper cell polarization shifts toward the Th17 phenotype under the influence of IL-6 and TNF- α , leading to increased production of IL-17A. IL-17A further amplifies inflammatory activity and enhances RANKL expression in osteoblasts and stromal cells, acting synergistically with IL-1 β to promote osteoclastogenesis.

This shift in bone metabolism is reflected by an increased RANKL/OPG ratio, indicating a transition from physiological bone remodeling to net bone resorption. Similar molecular patterns have been reported in periodontal disease progression²⁷, and are corroborated by elevated CTX-I levels detected in peri-implant crevicular fluid (PICF)^{12, 15}.

In parallel, a coordinated activation of matrix metalloproteinases (MMPs) occurs. Neutrophil-derived MMP-8 is primarily responsible for degradation of collagen types I and II in peri-implant soft tissues, whereas MMP-13, produced by osteoblast-lineage cells, is more specifically associated with degradation of type I collagen within mineralized bone structures. This sequential activation of proteolytic enzymes provides a mechanistic explanation for the temporal progression of biomarker expression and supports the rationale for staged molecular diagnostics.

4.2. Comparison with Previous Studies

The present findings are generally consistent with previous systematic reviews while also extending current knowledge in several important aspects.

The results align with Faot et al. (2015), who identified IL-1 β , TNF- α , and IL-6 as the most consistently elevated cytokines in peri-implant disease. However, comparatively fewer previous reviews have emphasized the role of IL-17A as a potential indicator of disease progression from mucositis to peri-implantitis²⁸.

Similarly, while Barros et al. (2016) reported that IL-1 β $\geq$ 50 pg/mL provides acceptable diagnostic accuracy in periodontal disease (sensitivity 81.3%, specificity 76.8%)¹⁴, the present review confirms a comparable pattern in peri-implant tissues. However, standardized diagnostic thresholds for peri-implant conditions remain to be established due to methodological variability across studies^{5, 24}.

Importantly, this review highlights the diagnostic relevance of the RANKL/OPG ratio, which demonstrated higher reported diagnostic performance (AUC 0.87–0.93) compared with individual cytokines, suggesting its potential utility as a more stable marker of bone resorption activity.

4.3. Molecular Markers of the Transition from Mucositis to Peri-Implantitis

This review identifies a cluster of molecular markers associated with the transition from reversible mucositis to irreversible peri-implantitis based on longitudinal evidence.

Key transition-associated biomarkers include:

- Increased IL-17A (4.5–10-fold), reflecting Th17 pathway activation
- Decreased IL-1Ra, indicating reduced anti-inflammatory control
- Increased MMP-13, associated with bone matrix degradation
- Appearance of CTX-I, indicating active osteoclastic bone resorption

Notably, several prospective studies suggest that these molecular alterations may precede clinical and radiographic manifestations by approximately 3–6 months, highlighting their potential utility for early diagnostic and preventive strategies.

4.4. Clinical Utility of Salivary Biomarkers

Compared with PICF, saliva exhibits lower specificity for peri-implant disease diagnosis due to its mixed origin and dilution by glandular secretions. Nevertheless, salivary biomarkers may provide clinically relevant information when analyzed using standardized protocols and multimarker approaches.

For example, the study by Sánchez-Jiménez et al. (2023) demonstrated that a four-marker salivary panel (IL-1 β , MMP-8, IL-6, osteopontin) achieved an AUC of 0.82, indicating moderate-to-good diagnostic performance²⁵. These findings support the potential role of saliva as a non-invasive screening tool, particularly in population-based or preventive settings.

4.5. Clinical Applicability and Threshold Considerations

Although no formal meta-analysis was performed, multiple studies reported recurring biomarker ranges that may serve as preliminary reference points for clinical interpretation. However, these values should be

considered indicative rather than validated diagnostic thresholds.

Reported PICF thresholds associated with peri-implantitis include:

- IL-1 β $\geq$ 50 pg/mL (risk indicator in selected cohorts)
- RANKL/OPG $\geq$ 1.2 (associated with onset of bone resorption)
- MMP-8 $\geq$ 80 ng/mL (active collagen degradation)
- IL-17A $\geq$ 12 pg/mL (transition phase marker)

For saliva:

- IL-1 β $\geq$ 25 pg/mL (moderate inflammation)
- MMP-8 $\geq$ 50 ng/mL (increased progression risk)
- Combined IL-1 β + MMP-8 panel: AUC 0.75–0.78

However, significant inter-study variability exists due to differences in sampling protocols, assay kits, calibration methods, and storage conditions, which limits direct comparability.

4.6. Standardization of Biomarker Assessment

A major limitation in biomarker research is methodological heterogeneity in sample collection and analysis.

For PICF, two main sampling approaches are used:

- Absorbent strips (Periopaper/PerioScan): standardized but prone to contamination and fluid dilution
- Microcapillary collection: more accurate but technically challenging and low-volume

For saliva, variability arises from:

- stimulated vs. unstimulated saliva
- whole saliva vs. gland-specific secretions
- circadian rhythm effects
- dietary and hydration status

Standardized protocols recommend morning collection (09:00–11:00), fasting state, oral rinse prior to sampling, and immediate freezing at -20°C .

4.7. Multimarker and Systems Biology Approaches

No single biomarker demonstrates sufficient diagnostic accuracy for standalone clinical application. Therefore,

multimarker panels combined with machine learning approaches represent a promising diagnostic strategy.

Distinct molecular subtypes of peri-implantitis have been proposed, including:

- IL-1 β -dominant inflammatory phenotype
- Th17/RANKL-dominant osteoclastic phenotype
- MMP- and CTX-I-driven hyper-destructive phenotype

Metabolomic studies further indicate alterations in salivary composition, including increased putrescine and cadaverine, reduced arginine availability, and altered organic acid profiles, reflecting microbial and host metabolic dysregulation²⁹.

4.8. Limitations of the Review

Several limitations should be acknowledged.

First, significant heterogeneity in study design, populations, and analytical methods precluded quantitative meta-analysis. Second, the predominance of cross-sectional studies (50.7%) limits causal inference regarding biomarker dynamics over time. Third, insufficient reporting of implant-related variables (surface characteristics, loading duration, and prosthetic design) restricted subgroup analyses.

Fourth, publication bias may have led to overrepresentation of studies with positive findings. Fifth, patient-related factors such as smoking status, systemic diseases, and oral hygiene were inconsistently reported. Finally, this review focused exclusively on PICF and saliva, excluding serum and other potential biomatrices.

5.1. Diagnostic Superiority of PICF

Peri-implant crevicular fluid (PICF) represents a more biologically specific diagnostic medium for peri-implantitis compared with mixed saliva, as it directly reflects local inflammatory activity and bone remodeling processes at the peri-implant site. Among the investigated biomarkers, interleukin-1 β (IL-1 β), receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio, and matrix metalloproteinase-8 (MMP-8) demonstrated the highest diagnostic performance in PICF, with reported AUC values ranging from 0.84 to 0.91, 0.87 to 0.93, and 0.80 to 0.88, respectively.

5.2. Diagnostic Potential of Saliva

Saliva demonstrates clinically relevant diagnostic utility, particularly when used in combination within multimarker panels and under standardized collection protocols. The combined assessment of salivary IL-1 β and MMP-8 yields a sensitivity of 73–78% and a specificity of 70–76% for peri-implantitis detection, supporting its potential application as a non-invasive screening tool in routine outpatient practice.

5.3. Molecular Indicators of Disease Progression

The transition from peri-implant mucositis to peri-implantitis is associated with a distinct molecular signature characterized by increased IL-17A expression (approximately 4.5–10-fold elevation) reflecting Th17-mediated immune activation, a marked reduction in IL-1 receptor antagonist (IL-1Ra), an elevated RANKL/OPG ratio exceeding 1.0, increased MMP-13 activity, and the emergence of CTX-I in PICP. These changes, reported in prospective studies, suggest a biologically plausible window for early therapeutic intervention prior to irreversible tissue destruction.

5.4. Recommendations for Future Research and Clinical Translation

To advance current findings toward clinically applicable diagnostic protocols, several key steps are required: (a) standardization of biomarker sampling methodologies, including control of circadian variation and procedural consistency; (b) large-scale, multicenter prospective validation studies to establish reliable diagnostic thresholds; (c) development and validation of commercially available multiplex biomarker assay systems; and (d) integration of biomarker-based diagnostics into established clinical guidelines, including those of the EFP and AAP.

5.5 Future Research Directions

Future investigations should focus on the development of advanced multimarker diagnostic models incorporating machine learning approaches to improve diagnostic accuracy and reproducibility. Longitudinal cohort studies with comprehensive clinical, radiographic, and molecular follow-up are essential to better characterize disease trajectories. Further research should also explore the interplay between systemic inflammatory status and local peri-implant biomarkers, particularly in patients with systemic conditions such as diabetes mellitus. Additionally, metabolomic and proteomic profiling may facilitate the identification of novel biomarkers and distinct molecular subtypes of peri-implantitis.

Practical Significance

The findings of this review provide a robust evidence-based foundation for the development of standardized biomarker-driven diagnostic strategies in implant dentistry. Such approaches have the potential to enable earlier identification of patients at risk for peri-implant disease before the onset of irreversible clinical and radiographic changes, thereby supporting timely preventive and minimally invasive therapeutic decision-making.

CONCLUSION

Current evidence indicates that peri-implant crevicular fluid provides greater diagnostic specificity than saliva for the assessment of peri-implant diseases. Biomarkers such as IL-1 β , MMP-8, IL-17A, and the RANKL/OPG ratio appear to be closely associated with inflammatory activity and disease progression. However, heterogeneity among the 31 included studies limits direct comparability of findings. Future prospective studies with standardized sampling and analytical protocols are required to establish clinically applicable diagnostic thresholds and improve the translational value of biomarker-based diagnostics in implant dentistry.

Zirconia implants represent a promising metal-free alternative with favorable esthetic properties, soft tissue integration, and reduced bacterial adhesion^{20,23,29,30}. These characteristics make zirconia particularly attractive in anterior esthetic regions and in patients seeking metal-free treatment solutions.

However, current evidence indicates greater variability in long-term survival and mechanical performance for zirconia implants compared with titanium systems^{28,41,45,47}. Limitations related to brittleness, low-temperature degradation, prosthetic flexibility, and limited long-term evidence continue to restrict their universal application. Therefore, implant material selection should be based on evidence-based clinical decision-making integrating biomechanical, esthetic, prosthetic, anatomical, and patient-related factors. Continued advancements in ceramic biomaterials and implant technology may further improve the predictability and clinical applicability of zirconia implant systems in the future.

DECLARATIONS

Conflict of Interest

The author declare no conflict of interest.

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Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

Author Contributions

The following describes the individual contributions of each author to this manuscript:

1 Abdulaeva Salihat Abakarovna initiated the research, developed the concept and structure of the review, and oversaw the writing and approval of the text.

2 Akhmedova Asiyat Akhmedovna conducted a systematic search and selection of scientific publications and performed a critical analysis of the empirical data on the main focus of the review.

3 Lazaryan Maria Nikolaevna conducted an analytical comparison of various scientific approaches and theoretical models presented in the literature.

4 Gadzhiev Baza Gasanovich synthesized the data obtained and formulated general conclusions and practical recommendations based on the analyzed sources.

5. Asvarova Gulnara Abilovna provided expert review of the methodological aspects of the review and verified the logical coherence of the arguments.

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7. Mirzekerimov Aivaz Meilanovich oversaw the editorial process and ensured that the text complied with the requirements of scientific style and publication format.

8. Omarov Murad Rashidovich conducted an analytical comparison of various scientific approaches and theoretical models presented in the literature.

9. Ordashev Khasan Alievich supervised the clinical case, provided expert consultation, and edited the final manuscript.

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CASE REPORT

WARTHIN TUMOR OF THE PAROTID GLAND: A CASE REPORT

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Abstract

Background: Warthin tumor (WT), also known as papillary cystadenoma lymphomatosum, is the second most common benign salivary gland neoplasm after pleomorphic adenoma. It accounts for approximately 5–15% of all salivary gland tumors and occurs predominantly in the parotid gland. The tumor mainly affects older adults and is strongly associated with tobacco smoking. Although modern imaging modalities and cytological techniques contribute significantly to preoperative assessment, histopathological examination remains the definitive diagnostic standard.

Case Presentation: A 70-year-old man presented with a slowly enlarging mass in the right parotid region associated with intermittent pain and local discomfort. His medical history was notable for chronic recurrent parotid sialadenitis and long-term tobacco use. Fine-needle aspiration biopsy revealed cystic-inflammatory material with a limited number of epithelial cells and no evidence of malignancy. Ultrasonography demonstrated multiple well-defined hypoechoic lesions with cystic components within the right parotid gland. The patient declined computed tomography and magnetic resonance imaging. Surgical excision was performed through a modified Blair incision using an extracapsular dissection technique with preservation of facial nerve function. Histopathological examination confirmed the diagnosis of Warthin tumor (ICD-O 8561/0). At 6-month follow-up, no evidence of recurrence was observed, and facial nerve function remained intact.

Conclusion: This case highlights the importance of integrating clinical, radiological, cytological, and histopathological findings in the evaluation of parotid gland masses. Despite advances in diagnostic imaging and cytology, histopathological examination remains essential for definitive diagnosis. Surgical excision provides both effective treatment and diagnostic confirmation, particularly in symptomatic patients or when diagnostic uncertainty persists.

Keywords: Warthin tumor; papillary cystadenoma lymphomatosum; parotid gland; extracapsular dissection; histopathology; case report

INTRODUCTION

Salivary gland tumors constitute a relatively uncommon group of head and neck neoplasms, accounting for approximately 3–6% of all tumors in this anatomical region¹. Approximately 65–80% of salivary gland tumors are benign, with pleomorphic adenoma and

Warthin tumor representing the most frequently encountered benign entities¹⁻⁴. Warthin tumor, first comprehensively described by Aldred Scott Warthin in 1929, is a benign epithelial salivary gland neoplasm characterized by oncocytic epithelial proliferation within a prominent lymphoid stroma^{1,5}.

According to the fifth edition of the World Health Organization (WHO) Classification of Head and Neck Tumours, Warthin tumor is categorized among benign epithelial tumors of oncocytic origin ⁶.

Epidemiological studies indicate that Warthin tumor accounts for approximately 11% of all salivary gland neoplasms and nearly 17% of benign salivary gland tumors, making it the second most common benign salivary gland tumor after pleomorphic adenoma⁴. The lesion develops almost exclusively in the parotid gland, particularly within its tail region. Multifocal or bilateral involvement has been reported in approximately 5–15% of cases ^{1,2,13}.

The pathogenesis of Warthin tumor remains incompletely understood. The most widely accepted theory suggests that salivary ductal epithelial inclusions become entrapped within intraparotid lymphoid tissue during embryogenesis⁷.

Subsequent oncocytic metaplasia, mitochondrial accumulation, cystic degeneration, and local immunological mechanisms may contribute to tumor formation ^{7,8}.

Tobacco smoking is regarded as the strongest recognized risk factor associated with Warthin tumor. Multiple studies have demonstrated a substantially increased incidence among smokers compared with non-smokers ⁹⁻¹³. Additional factors associated with disease development include advanced age, male sex, and chronic inflammatory disorders of the salivary glands ^{2,13}.

Clinically, Warthin tumor typically presents as a slowly enlarging, mobile, well-circumscribed, and generally painless mass in the parotid region ^{1,2}. Some patients may experience pain, pressure sensation, tenderness, or inflammatory symptoms, particularly in the presence of cystic degeneration or secondary inflammation ^{2,13}.

The diagnosis relies on the integration of clinical, radiological, cytological, and histopathological findings. Ultrasonography is considered the first-line imaging modality, while CT and MRI provide valuable information regarding tumor extent and adjacent anatomical structures ^{10,11}.

Fine-needle aspiration biopsy (FNAB) is frequently used preoperatively; however, its diagnostic accuracy may be reduced in lesions exhibiting extensive cystic changes ^{3,9,14,15}.

Current management strategies depend on tumor size, symptoms, patient age, and diagnostic certainty.

Although active surveillance has been proposed for selected asymptomatic patients, surgical excision remains the most widely accepted treatment approach ^{3,5,14}.

Common surgical techniques include extracapsular dissection, partial parotidectomy, and superficial parotidectomy, all aiming to achieve complete tumor removal while preserving facial nerve function ^{5,14}.

The aim of the present case report is to describe the clinical presentation, diagnostic evaluation, histopathological findings, and surgical management of a Warthin tumor occurring in a 70-year-old male patient.

2. Case Presentation

A 70-year-old male was referred to the Department of Oral and Maxillofacial Surgery with complaints of a slowly enlarging mass in the right parotid region associated with intermittent pain and local discomfort.



Figure 1. Clinical appearance of the right parotid swelling before surgery.

According to the patient, the lesion had first been noticed several years earlier. Because of its slow growth and the absence of significant symptoms, he did not initially seek medical attention. During the months preceding presentation, however, the patient observed gradual enlargement of the swelling accompanied by intermittent pain, a sensation of pressure, and increasing discomfort in the right parotid area. He also reported mild xerostomia and subjective alterations in salivary taste.

The patient's medical history was notable for chronic recurrent right-sided parotid sialadenitis, for which he had previously received multiple courses of conservative treatment. The inflammatory episodes had been characterized by recurrent swelling and discomfort in the affected gland.

In addition, the patient reported a long-term smoking history. Chronic inflammatory stimulation and tobacco exposure have both been implicated as potential contributing factors in the pathogenesis of Warthin tumor and may promote oncocytic alterations within salivary gland tissue ^{1,5,13}.

General physical examination revealed no significant systemic abnormalities. The patient's overall condition was satisfactory, and vital signs were within normal limits. External examination of the head and neck demonstrated mild asymmetry of the right parotid region caused by localized soft tissue enlargement. The overlying skin appeared normal, without erythema, ulceration, discoloration, or signs of acute inflammation.

Palpation revealed several well-circumscribed, mobile, moderately firm nodular lesions located within the inferior aspect of the right parotid gland. The lesions were mildly tender on palpation but were not fixed to surrounding tissues. No fluctuation or signs of abscess formation were detected.

Particular attention was paid to facial nerve assessment. Clinical examination demonstrated intact facial nerve function, with symmetrical facial movements and no evidence of motor weakness or paralysis involving any facial muscle group.

Palpation of the cervical lymph node chains revealed no pathological enlargement or tenderness. Intraoral examination showed healthy oral mucosa without visible pathological changes. Mild xerostomia was observed, but no purulent discharge from Stensen's duct or other signs of active salivary gland infection were identified.

Based on the clinical findings, a benign salivary gland neoplasm was suspected. The initial differential diagnosis included Warthin tumor, pleomorphic adenoma, oncocytoma, lymphoepithelial cyst, chronic sialadenitis, and low-grade salivary gland malignancies. Fine-needle aspiration biopsy (FNAB) was subsequently performed. Cytological examination revealed predominantly cystic-inflammatory material containing inflammatory cells and a limited number of epithelial elements.

No cytological evidence of malignancy was identified. However, the specimen was considered non-diagnostic because the number of characteristic oncocytic epithelial cells was insufficient for definitive cytological classification. Such findings have been frequently reported in Warthin tumors with extensive cystic degeneration, where aspiration samples may

contain predominantly fluid and inflammatory components rather than representative epithelial elements ^{3,9,12}.

Subsequently, ultrasonographic examination of the right parotid gland was performed. Sonographic assessment demonstrated structural alterations within the gland and multiple well-defined hypoechoic lesions, some of which exhibited cystic components. The lesions showed regular margins and a heterogeneous internal architecture consistent with mixed cystic and solid composition. No evidence of infiltration into adjacent soft tissues was observed. These findings were highly suggestive of Warthin tumor and corresponded closely to the characteristic ultrasonographic appearance described in the literature ¹⁰.



Figure 2. Ultrasonographic image demonstrating multiple hypoechoic lesions with cystic components within the

For further evaluation and preoperative planning, computed tomography (CT) and magnetic resonance imaging (MRI) were recommended. However, the patient declined both investigations because of claustrophobia and difficulty remaining motionless for prolonged periods. Although cross-sectional imaging is widely used in the assessment of salivary gland tumors, several studies have demonstrated that high-resolution ultrasonography may provide sufficient diagnostic information in cases involving superficially located lesions with a high probability of benignity ^{10,11}.

Following multidisciplinary evaluation and detailed discussion with the patient, surgical treatment was recommended. The decision was based on the presence of pain, progressive enlargement of the lesion, the inconclusive FNAB findings, and the need for definitive histopathological diagnosis. After obtaining informed consent, surgical excision was scheduled. The procedure was performed under general anesthesia. Access to the lesion was achieved through a modified Blair incision, a standard surgical approach widely used in parotid gland surgery because it provides excellent exposure while facilitating preservation of the facial nerve and satisfactory cosmetic outcomes ¹⁴.



Figure 3. Preoperative marking of the modified Blair incision on the skin surface prior to parotid surgery.

After elevation of the skin flap and careful dissection of the superficial parotid tissues, the lesion was identified within the inferior portion of the gland. Particular attention was directed toward identification and preservation of the facial nerve branches throughout the procedure. The tumor was well circumscribed and separated from surrounding tissues without evidence of infiltration.

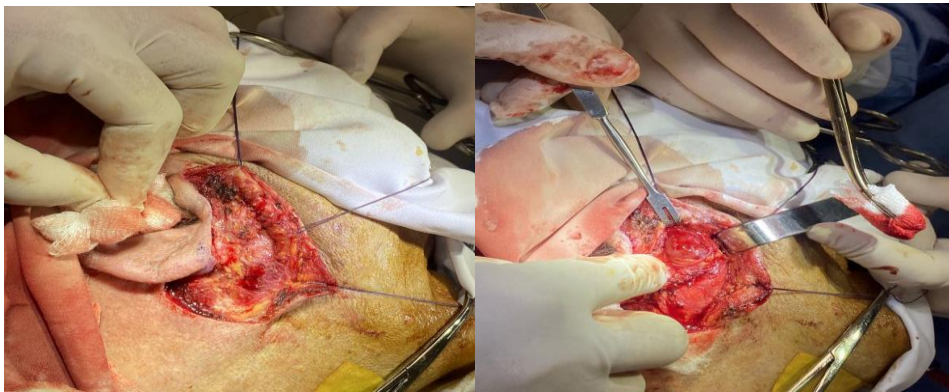


Figure 4. a,b Intraoperative formation of the skin-subcutaneous flap following the modified Blair incision using combined blunt and sharp dissection techniques.

Complete excision was achieved using an extracapsular dissection technique, allowing removal of the lesion while preserving the surrounding healthy parotid tissue and maintaining facial nerve integrity^{5,14}. Several adjacent nodular lesions identified within the same region were also excised. Intraoperative inspection demonstrated no evidence of local invasion or suspicious malignant features.

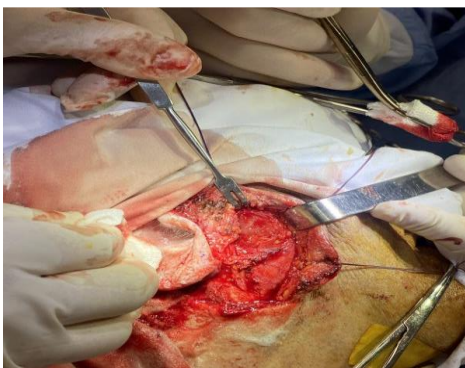


Figure 5. Surgical exposure of the parotid gland after skin flap elevation and superficial parotid dissection, revealing a well-circumscribed lesion in the inferior pole of the gland

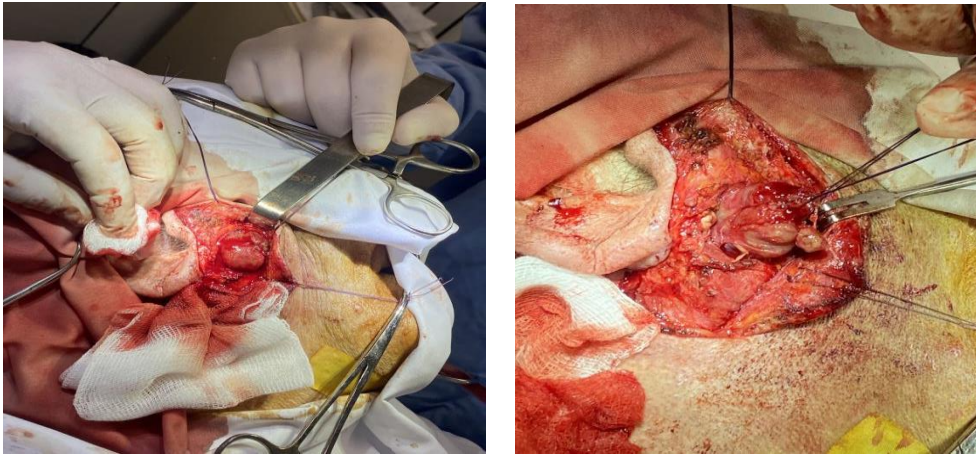


Figure 6. a, b Intraoperative identification of multiple tumor nodules within the parotid gland. The lesions were meticulously dissected from the surrounding tissues using combined blunt and sharp techniques with preservation of adjacent anatomical structures, followed by complete enucleation within their capsular boundaries.



Figure 7. Intraoperative photograph showing complete enucleation of the tumor nodules together with their intact capsules.

Figure 8. Gross surgical specimen showing the excised parotid tumor nodules.

Following complete removal of the lesion, meticulous hemostasis was achieved. A passive drain was inserted, and layered closure of the surgical wound was performed. A compressive dressing was subsequently applied. The postoperative course was uneventful. No hemorrhage, hematoma, salivary fistula, wound infection, or other early postoperative complications were observed. The patient's general condition remained stable throughout hospitalization.

Particular attention was directed toward postoperative facial nerve evaluation. Clinical examination confirmed complete preservation of facial nerve function, with normal symmetrical facial movements and no evidence of temporary or permanent motor dysfunction. This outcome is consistent with previously reported results following surgical treatment of benign parotid gland tumors ¹⁴.

At 6-month follow-up, no evidence of tumor recurrence was observed, and facial nerve function remained fully intact without any signs of functional impairment.

The excised specimen was submitted for histopathological examination to establish the definitive diagnosis.

3. Histopathological Findings

The excised specimen was submitted for histopathological examination. Gross examination revealed a well-circumscribed cystic-solid lesion surrounded by a thin fibrous capsule. The cut surface demonstrated multiple cystic spaces containing brownish fluid and papillary projections.

Microscopic examination demonstrated cystic cavities lined by a characteristic bilayered oncocytic epithelium. The luminal layer consisted of tall columnar oncocytic cells with abundant eosinophilic granular cytoplasm, whereas the basal layer was composed of cuboidal epithelial cells. Numerous papillary projections extended into the cystic lumen. The epithelial structures were supported by a dense lymphoid stroma containing numerous reactive lymphoid follicles and prominent germinal centers. No significant cytological atypia, increased mitotic activity, necrosis, or invasive growth pattern was observed.

These findings were entirely consistent with Warthin tumor (papillary cystadenoma lymphomatosum; ICD-O 8561/0) according to current WHO diagnostic criteria ^{6,8}.

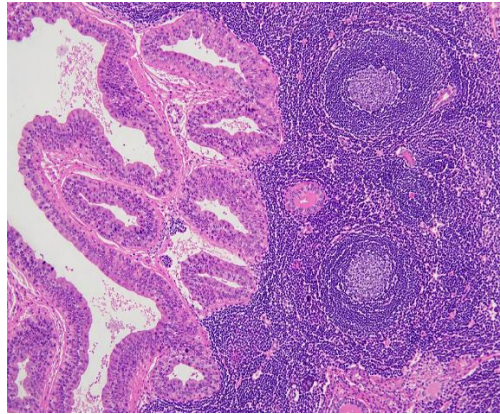


Figure 9. Histopathological photomicrograph of Warthin tumor demonstrating characteristic bilayered oncocytic epithelium forming papillary projections and a dense lymphoid stroma containing reactive lymphoid follicles and germinal centers (H&E stain, original magnification $\times 100$).

Microscopic evaluation of the surgical margins confirmed complete excision (R0 resection). No evidence of malignant transformation was identified ^{6,8}.

The combined clinical, radiological, surgical, and histopathological findings established the definitive diagnosis of Warthin tumor of the right parotid gland

4. DISCUSSION

Warthin tumor (papillary cystadenoma lymphomatosum) is the second most common benign salivary gland neoplasm after pleomorphic adenoma and occurs almost exclusively within the parotid gland ^{1,4,6}. Despite its benign biological behavior, this tumor continues to attract considerable clinical interest because of its distinctive histopathological characteristics, strong association with tobacco smoking, tendency toward multifocal and bilateral occurrence, and the evolving concepts regarding its diagnosis and management ^{2,5,13,16}.

The present case demonstrated several clinical and pathological features characteristic of Warthin tumor. The patient was a 70-year-old male, corresponding to the typical demographic profile reported in the literature. Epidemiological studies consistently indicate that Warthin tumor occurs predominantly during the sixth to eighth decades of life and remains particularly common among older men ^{2,13}.

Although the historical male predominance has diminished in recent decades due to changing smoking habits, elderly men continue to constitute the most frequently affected patient population^{13,18}.

An important feature of the present case was the patient's smoking history. Tobacco smoking is considered the most significant environmental risk factor associated with Warthin tumor development. Smokers have been reported to exhibit a several-fold increased risk of developing this neoplasm compared with non-smokers¹³. Current pathogenetic theories suggest that chronic exposure to tobacco-derived carcinogens induces oncocyctic metaplasia, mitochondrial DNA alterations, oxidative stress, and epithelial injury within salivary gland tissue, thereby facilitating tumorigenesis. Recent molecular investigations have further demonstrated genetic alterations, including KRAS codon 12 mutations, in subsets of proliferating and metaplastic Warthin tumors, suggesting that at least some lesions may represent true neoplastic proliferations rather than purely reactive processes¹⁹.

The coexistence of chronic recurrent parotid sialadenitis in the present patient deserves particular attention. Although the exact etiology of Warthin tumor remains controversial, chronic inflammatory stimulation has been proposed as a potential contributing factor in tumor development^{7,8}. Recurrent inflammatory episodes may induce epithelial metaplasia and modify the local lymphoid microenvironment, creating conditions favorable for oncocyctic transformation⁸. While a direct causal relationship between chronic sialadenitis and Warthin tumor has not been definitively established, the clinical findings observed in the present case are compatible with contemporary pathogenetic hypotheses.

Clinically, the lesion presented as a slowly enlarging parotid mass associated with intermittent pain and local discomfort. This presentation corresponds well with previous reports describing Warthin tumor as a slowly growing, mobile, and well-circumscribed lesion^{1,2}. Pain is considered a relatively uncommon symptom and is usually associated with secondary inflammation, infarction, hemorrhage, or cystic degeneration^{2,13}. Therefore, the painful presentation observed in the present patient may be considered an atypical but well-recognized manifestation.

Fine-needle aspiration biopsy (FNAB) remains an important component of preoperative evaluation; however, its limitations must be recognized. In the present case, FNAB yielded predominantly cystic-

inflammatory material and only a limited number of epithelial cells. Similar findings have been frequently reported in Warthin tumors exhibiting prominent cystic architecture^{3,9,12}. A recent systematic review and meta-analysis by Fisher and Ronen confirmed that although FNAB demonstrates generally high diagnostic accuracy for Warthin tumor, false-negative and indeterminate results remain possible, particularly in cystic lesions or when insufficient oncocyctic material is obtained¹⁵. Consequently, FNAB findings should always be interpreted in conjunction with clinical and radiological information.

Imaging studies also contributed substantially to diagnostic evaluation. Ultrasonography revealed multiple well-circumscribed hypoechoic lesions containing cystic components, findings that are highly characteristic of Warthin tumor¹⁰. Similar sonographic appearances have been consistently reported in previous radiological studies¹⁰. The patient declined CT and MRI examinations, which limited further radiological characterization. Nevertheless, several authors have demonstrated that ultrasonography may provide sufficient information for treatment planning in selected patients with superficial lesions and a high likelihood of benign disease^{10,11}.

Recent advances in radiomics and artificial intelligence have further improved imaging-based differentiation of parotid tumors. Feng et al. developed a multicenter CT-radiomics model capable of distinguishing Warthin tumor from pleomorphic adenoma with high diagnostic accuracy, suggesting that advanced imaging analysis may contribute to more precise preoperative diagnosis in the future²⁰. Although such technologies were not available in the present case, they represent promising developments for salivary gland tumor diagnostics.

The differential diagnosis of Warthin tumor remains broad and includes pleomorphic adenoma, oncocytoma, basal cell adenoma, lymphoepithelial cyst, low-grade mucoepidermoid carcinoma, and acinic cell carcinoma^{3,6}. Considerable overlap may exist among these entities regarding both imaging and cytological findings. Consequently, definitive diagnosis frequently depends upon histopathological examination.

Histopathological assessment remains the gold standard for diagnosis. In the present case, microscopic examination demonstrated all classical diagnostic features, including cystic spaces lined by bilayered oncocyctic epithelium, papillary epithelial projections, and a dense lymphoid stroma containing reactive follicles and germinal centers. These findings fully satisfy the current WHO diagnostic criteria for Warthin

tumor^{4,6}. Recent historical and pathological reviews continue to emphasize that the coexistence of oncocytic epithelium and prominent lymphoid stroma remains the defining microscopic hallmark of this lesion¹⁸.

Management strategies for Warthin tumor have evolved considerably during recent years. Historically, surgical excision has been regarded as the standard treatment modality. However, increasing evidence supports active surveillance in selected patients with asymptomatic tumors and highly reliable preoperative diagnoses^{5,16}. Nishimura et al., in a retrospective analysis of 387 cases with more than two decades of clinical experience, concluded that observation may represent a safe alternative in carefully selected patients, particularly elderly individuals with significant comorbidities and stable tumors¹⁶. Nevertheless, successful conservative management requires high diagnostic certainty and rigorous follow-up protocols.

In the present case, surgical treatment was considered the most appropriate option because the patient experienced pain, the preoperative diagnosis remained uncertain, and multiple lesions were identified. These factors correspond closely with contemporary indications for surgery^{3,16}. Complete excision was achieved while preserving facial nerve function. Preservation of the facial nerve remains one of the principal objectives of parotid surgery because postoperative dysfunction can significantly affect quality of life¹⁴.

Recent long-term clinical studies have reported excellent outcomes following surgical management. Bonavolontà et al. analyzed 224 surgically treated Warthin tumors and demonstrated low recurrence rates together with excellent long-term functional outcomes¹⁷. Similar results were observed in the present case, in which complete excision and preservation of facial nerve integrity were achieved without postoperative complications.

Recurrence after adequate surgical treatment is uncommon and is generally attributed to multifocal disease or the development of metachronous tumors rather than true local recurrence^{2,5,13,17}. Likewise, malignant transformation remains exceptionally rare, occurring in fewer than 1% of cases. No histopathological evidence of dysplasia or malignant transformation was identified in the present patient.

Overall, the present case reinforces the importance of a multidisciplinary diagnostic approach integrating clinical examination, imaging findings, cytological assessment, surgical evaluation, and histopathological

confirmation. Despite substantial advances in imaging technologies, molecular pathology, and minimally invasive diagnostic techniques, histopathological examination remains the definitive diagnostic standard. Furthermore, surgical excision continues to represent a reliable and effective treatment option, particularly in symptomatic patients or in cases where diagnostic uncertainty persists despite comprehensive preoperative assessment^{3,5,6,16,17}.

Recent molecular and radiological advances continue to improve the understanding and preoperative characterization of Warthin tumor. Nevertheless, none of the currently available diagnostic modalities can completely replace histopathological examination, which remains essential for definitive diagnosis and exclusion of malignant transformation.

Limitations

The present case report has several limitations:

1. The patient declined CT and MRI examinations, which limited the extent of preoperative radiological assessment.
2. This report describes a single clinical case; therefore, the findings cannot be generalized to larger patient populations.
3. Although a 6-month follow-up period demonstrated no recurrence and preserved facial nerve function, longer-term follow-up is required to fully assess the risk of metachronous lesions and late recurrence.
4. Detailed information regarding the patient's smoking history was unavailable, preventing assessment of the influence of the principal recognized risk factor for Warthin tumor in this particular case.

CONCLUSION

Warthin tumor is a common benign neoplasm of the parotid gland that predominantly affects older adults, particularly men. The present case demonstrates that even in the setting of limited preoperative imaging data, surgical management followed by histopathological examination can establish a definitive diagnosis and provide effective treatment. Early recognition, appropriate surgical planning, and histopathological confirmation remain essential for achieving favorable clinical outcomes. Surgical excision continues to represent a reliable and effective treatment modality, particularly in symptomatic patients or in cases where diagnostic uncertainty persists despite preoperative investigations.

DECLARATIONS

Competing Interests

The authors declare no conflict of interest.

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Ethical Approval

Informed consent was obtained from patients. Clinical case approved in accordance with ethical standards.

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CASE SERIES

CLINICAL, CYTOLOGICAL, AND HISTOPATHOLOGICAL ALTERATIONS OF DENTURE-BEARING ORAL MUCOSA IN WOMEN WITH CERVICAL CANCER USING REMOVABLE DENTURES: A RETROSPECTIVE CLINICAL CASE SERIES**Vahe Azatyan¹, Arpine Sargsyan², Marine Voskanyan³, Gagik Khachatryan⁴, Nvard Vanyan⁵**

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ABSTRACT

Background: Cervical cancer remains among the most common malignant neoplasms affecting women worldwide. In addition to systemic complications, both the disease itself and its treatment may induce significant pathological alterations within the oral cavity. Patients using removable dentures are particularly susceptible to inflammatory and dystrophic changes of the denture-bearing mucosa due to chronic mechanical irritation, immune dysfunction, and treatment-related toxicity. The present study aimed to evaluate the clinical, cytological, and histopathological characteristics of denture-bearing oral mucosa in women with cervical cancer.

Methods: A retrospective clinical case series was conducted involving 17 women diagnosed with cervical cancer who used complete or partial removable dentures. Clinical examination, cytological assessment, and histopathological evaluation were performed according to standardized diagnostic protocols. Oral manifestations, denture-related factors, and microscopic tissue alterations were analyzed.

Results: The mean age of the patients was 63.4 ± 6.8 years. The most frequent clinical findings included diffuse erythema (88.2%), chronic inflammation (88.2%), xerostomia (82.4%), edema (76.5%), vascular abnormalities (76.5%), hyperkeratosis (58.8%), and epithelial atrophy (52.9%). Cytological examination demonstrated epithelial degeneration, neutrophilic infiltration, and parakeratosis. Histopathological analysis revealed acanthosis, parakeratosis, basal cell degeneration, chronic lymphoplasmacytic infiltration, vascular congestion, and connective tissue fibrosis. No cytological or histopathological evidence of malignant transformation was identified.

Conclusions: Women with cervical cancer using removable dentures frequently present with inflammatory, vascular, and dystrophic alterations of the denture-bearing mucosa. These changes most likely result from combined effects of malignant disease, anticancer therapy, salivary dysfunction, immune dysregulation, and chronic mechanical irritation associated with removable prostheses. Multidisciplinary management is essential to reduce complications and improve oral health-related quality of life.

Keywords: cervical cancer; oral mucosa; denture-bearing mucosa; removable dentures; prosthetic stomatitis

INTRODUCTION

Cervical cancer remains one of the most significant malignant diseases affecting women worldwide and continues to represent a major cause of cancer-related morbidity and mortality despite substantial advances in prevention, screening, and therapeutic strategies¹⁻³. According to recent global cancer statistics, cervical cancer remains among the most frequently diagnosed malignancies in women, particularly in low- and middle-income countries where access to preventive healthcare services and organized screening programs is limited⁴⁻⁶.

Advances in surgical oncology, chemotherapy, radiotherapy, and combined chemoradiotherapy have significantly improved survival outcomes. However, treatment-related adverse effects continue to present a considerable clinical challenge. Among these complications, oral manifestations are frequently encountered and may persist long after completion of oncological therapy. Oral mucositis, xerostomia, opportunistic infections, and chronic inflammatory lesions of the oral cavity significantly affect patients' quality of life, treatment tolerance, and nutritional status⁷⁻¹⁰. The oral mucosa is a highly dynamic tissue characterized by continuous epithelial turnover and close interaction with the immune system and oral microbiota. Consequently, it is particularly vulnerable to pathological changes associated with systemic disease, immune dysfunction, metabolic disturbances, vascular impairment, and the toxic effects of cancer therapy^{11,12}. Numerous studies have reported that patients undergoing oncological treatment frequently develop oral complications, including mucositis, xerostomia, dysgeusia, opportunistic infections, periodontal deterioration, and chronic inflammatory lesions of the oral mucosa¹³⁻¹⁷.

These conditions may impair oral function, speech, nutritional intake, and the success of subsequent prosthetic rehabilitation^{18,19}.

In clinical practice, patients using removable dentures present additional challenges. The denture-bearing mucosa is continuously exposed to mechanical loading, frictional forces, microbial biofilm accumulation, and functional stress²⁰⁻²³. Under physiological conditions, adaptive mechanisms maintain tissue integrity; however, in systemic disease and immunocompromised states, the ability of oral tissues to respond to chronic irritation may be significantly reduced, leading to inflammatory and degenerative changes in the supporting mucosa. Immune dysregulation associated with malignant disease plays a crucial role in the development of oral complications²⁴. Both cancer and anticancer therapies affect cellular immunity, cytokine balance, epithelial turnover, and

tissue repair mechanisms. Chemotherapeutic agents exert cytotoxic effects on rapidly proliferating epithelial cells, whereas radiotherapy induces vascular injury, fibrosis, salivary gland dysfunction, and reduced regenerative capacity²⁵⁻²⁷. Collectively, these factors increase susceptibility to mucosal injury and delay healing processes.

Xerostomia is one of the most common oral complications in oncology patients and is frequently associated with significant functional impairment²⁸⁻³⁰. Reduced salivary secretion compromises lubrication, buffering capacity, antimicrobial defense, and mucosal protection. In denture wearers, xerostomia increases frictional trauma, promotes microbial colonization, and contributes to denture-associated stomatitis and chronic mucosal inflammation³¹⁻³³.

Previous studies have demonstrated that chronic denture-related irritation may lead to epithelial hyperplasia, acanthosis, parakeratosis, dyskeratosis, inflammatory infiltration, and connective tissue remodeling³⁴⁻³⁶. In patients with a history of cancer and oncological treatment, these pathological processes may be further intensified by immune dysfunction and treatment-related tissue toxicity. Although oral mucositis and cancer therapy-related oral complications have been extensively investigated^{13-19,41}, relatively little attention has been given to the specific clinical and histopathological alterations of denture-bearing mucosa in women with cervical cancer. A more detailed understanding of these changes may facilitate early detection, improved prosthetic management, and development of preventive strategies.

Therefore, the aim of this retrospective clinical case series was to evaluate the clinical, cytological, and histopathological alterations of denture-bearing oral mucosa in women with cervical cancer using removable dentures.

MATERIALS AND METHODS

Study Design and Patient Population

This retrospective clinical case series was conducted at the Department of Prosthodontics and Oral Pathology between January 2021 and January 2025. The study aimed to evaluate clinical, cytological, and histopathological alterations of denture-bearing oral mucosa in women with cervical cancer using removable dentures.

A total of 17 female patients with histologically confirmed cervical cancer were included in the study. All participants had completed oncological treatment before dental evaluation and were referred for assessment because of oral symptoms and mucosal alterations associated with removable prosthetic rehabilitation.

Table 1. Baseline Characteristics of the Study Population (n = 17)

Variable	Value
Number of patients	17
Sex	Female (100%)
Mean age, years (range)	61.8 (54–72)
Histologically confirmed cervical cancer	17 (100%)
Previous radiotherapy	17 (100%)
Previous chemotherapy	17 (100%)

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Female sex	Autoimmune oral diseases
Histologically confirmed cervical cancer	Uncontrolled diabetes mellitus
Use of complete or partial removable dentures for ≥ 1 year	Non-denture-related oral infections
Presence of oral symptoms or mucosal lesions	Previous head and neck malignancies
	Active tobacco use

Clinical Assessment

All patients underwent a comprehensive oral examination performed by experienced prosthodontists and oral pathologists. Clinical evaluation included assessment of mucosal erythema, edema, hyperkeratosis, epithelial atrophy, petechial hemorrhages, salivary flow reduction, denture stability, and denture hygiene status. Standardized intraoral clinical photographs were obtained for documentation and comparative assessment.

Cytological Assessment

Exfoliative cytological samples were collected from representative mucosal lesions using a cytobrush technique. Smears were processed according to standard cytological protocols and examined microscopically. Particular attention was directed toward epithelial degeneration, inflammatory cell infiltration, keratinization abnormalities, epithelial maturation disturbances, and the presence of cellular atypia.

Histopathological Examination

Incisional biopsy specimens were obtained from representative lesions when clinically indicated. Tissue samples were fixed in 10% neutral-buffered formalin, routinely processed, embedded in paraffin, sectioned at 4 μ m, and stained with hematoxylin and eosin.

Histopathological evaluation focused on epithelial thickness, acanthosis, parakeratosis, basal cell degeneration, inflammatory infiltration, vascular alterations, connective tissue fibrosis, and other structural changes of the oral mucosa.

RESULTS**Clinical Findings**

All 17 patients reported oral discomfort, burning sensation, xerostomia, denture intolerance, and varying degrees of chronic mucosal irritation. Clinical examination demonstrated a high prevalence of inflammatory and dystrophic changes affecting the denture-bearing mucosa. Diffuse erythema and chronic inflammatory changes were the most common findings, each observed in 15 of 17 patients (88.2%). Xerostomia was present in 14 patients (82.4%), while edema and vascular abnormalities were identified in 13 patients (76.5%). Hyperkeratosis and epithelial atrophy were observed less frequently but remained common findings within the study population. Localized traumatic lesions were most commonly associated with poor denture hygiene, prosthetic instability, or occlusal discrepancies.

Clinical findings in denture-wearing women with cervical cancer

Clinical finding	n (%)
Diffuse erythema	15 (88.2)
Chronic inflammation	15 (88.2)
Xerostomia	14 (82.4)
Edema	13 (76.5)
Vascular abnormalities	13 (76.5)
Hyperkeratosis	10 (58.8)
Epithelial atrophy	9 (52.9)
Petechial hemorrhages	8 (47.1)
Traumatic lesions	7 (41.2)

Note: Traumatic lesions were predominantly associated with poor denture hygiene, prosthetic instability, and occlusal discrepancies.

Cytological Findings

Cytological examination demonstrated predominantly degenerative epithelial changes accompanied by moderate inflammatory activity. The most common findings included epithelial cell degeneration, neutrophilic infiltration, and parakeratosis, along with impaired epithelial maturation. No cytological evidence of epithelial dysplasia or malignant transformation was observed in any case.

Table 3. Cytological findings in denture-bearing mucosa

Cytological parameter	n (%)
Epithelial degeneration	15 (88.2)
Neutrophilic infiltration	13 (76.5)
Parakeratosis	12 (70.6)
Disturbed epithelial maturation	11 (64.7)
Macrophage accumulation	7 (41.2)
Cellular atypia	0 (0)
Malignant cells	0 (0)

Note: No cytological evidence of dysplasia or malignancy was detected.

Histopathological Findings

Histopathological analysis revealed a consistent pattern of chronic inflammatory and dystrophic alterations in the denture-bearing oral mucosa. The most frequent microscopic features included acanthosis, parakeratosis, chronic lymphoplasmacytic infiltration, vascular congestion, and connective tissue fibrosis. Additionally, basal cell degeneration and focal epithelial atrophy were observed in a subset of patients, reflecting persistent mucosal irritation and impaired tissue homeostasis.

Table 4. Histopathological findings in denture-bearing oral mucosa

Histopathological feature	n (%)
Acanthosis	15 (88.2)
Parakeratosis	14 (82.4)
Chronic lymphoplasmacytic infiltration	14 (82.4)
Vascular congestion	13 (76.5)
Connective tissue fibrosis	12 (70.6)
Basal cell degeneration	11 (64.7)
Epithelial atrophy	9 (52.9)

Overall, the histopathological findings were consistent with chronic inflammatory-dystrophic alterations of the denture-bearing oral mucosa, reflecting the combined effects of chronic prosthetic irritation, xerostomia, impaired tissue regeneration, and previous oncological treatment.

REPRESENTATIVE CLINICAL CASE

To illustrate the clinical, cytological, and histopathological findings observed in the study cohort, a representative case is presented below. This patient was selected because the observed manifestations closely reflected the most common clinical and morphological features identified among the women included in the present case series.

A 61-year-old woman was referred to the Department of Prosthodontics with complaints of persistent oral burning sensation, mucosal tenderness, xerostomia, and discomfort during mastication associated with the use of a complete maxillary removable acrylic denture. The symptoms had gradually progressed over the preceding six months and had significantly affected oral comfort, masticatory function, and prosthesis tolerance. The patient's medical history was notable for stage IIIB cervical cancer diagnosed three years earlier. She had undergone combined oncological treatment consisting of external beam radiotherapy and platinum-based chemotherapy. A complete maxillary removable denture had been worn continuously for approximately three years. No history of diabetes mellitus, autoimmune disease, or tobacco use was reported.

Clinical Examination

Intraoral examination revealed extensive pathological alterations involving the denture-bearing mucosa of the maxilla. Diffuse erythema and edema were present throughout the palatal mucosa and were associated with marked tenderness on palpation. Multiple hyperkeratotic plaques were observed in the hard palate region, while several areas demonstrated focal epithelial atrophy characterized by thinning of the mucosa and reduced tissue resilience.

Numerous petechial hemorrhages were identified within the denture-bearing area, suggesting increased vascular fragility and disturbances of local microcirculation. Clinical evaluation also demonstrated a pronounced reduction in salivary secretion, which corresponded with the patient's subjective complaints of persistent oral dryness.





Figure 1a,b. Denture-bearing oral mucosa demonstrating diffuse erythema, petechial hemorrhages, xerostomia-related changes, and chronic mechanical irritation associated with prolonged denture use.

Examination of the removable denture revealed inadequate hygiene with visible plaque accumulation, signs of occlusal imbalance, and insufficient adaptation of the prosthetic borders. These factors were considered potential contributors to chronic mucosal irritation and ongoing inflammatory changes.



Figure 2. Complete maxillary removable denture showing inadequate hygiene, plaque accumulation, and occlusal discrepancies contributing to chronic prosthetic trauma.

Overall, the clinical findings were consistent with a chronic inflammatory-dystrophic process affecting the denture-bearing mucosa. The observed alterations were likely influenced by the combined effects of previous oncological treatment, treatment-related xerostomia, impaired tissue regeneration, and persistent prosthetic irritation.

Cytological Findings

Exfoliative cytological examination demonstrated numerous degenerative epithelial cells exhibiting nuclear and cytoplasmic alterations. Moderate neutrophilic inflammatory infiltration was present, accompanied by scattered macrophages. Focal areas of parakeratosis and disturbed epithelial maturation were also identified.

No cytological evidence of dysplasia or malignant transformation was observed.

Histopathological and Morphological Findings

Incisional biopsy specimens obtained from representative areas of the palatal mucosa were submitted for histopathological examination. Microscopic evaluation revealed pronounced acanthosis of the stratified squamous epithelium with irregular epithelial thickening. Focal areas of parakeratosis were present, indicating abnormal keratinization associated with chronic irritation.

In contrast, other regions demonstrated epithelial thinning and focal atrophy, suggesting impaired regenerative capacity. Degenerative alterations of the basal cell layer were characterized by cytoplasmic vacuolization and disruption of normal cellular organization.

The underlying connective tissue exhibited moderate chronic lymphoplasmacytic inflammatory infiltration. Prominent vascular alterations were observed, including vascular dilation and congestion consistent with impaired microcirculation. Areas of connective tissue fibrosis were also identified, reflecting long-standing inflammatory activity and chronic tissue remodeling.

Taken together, the microscopic findings demonstrated a combination of inflammatory, vascular, and dystrophic alterations characteristic of chronic prosthetic stomatitis in a patient with a history of cervical cancer and previous oncological treatment.

The differential diagnosis included denture-associated stomatitis, chronic traumatic mucositis, oral candidiasis, contact hypersensitivity reactions, and potentially premalignant epithelial lesions. Histopathological examination excluded dysplastic and malignant epithelial changes.

Final Diagnosis

Clinical diagnosis: Chronic prosthetic stomatitis associated with treatment-related xerostomia and impaired mucosal adaptation following cervical cancer therapy.

Histopathological diagnosis: Chronic inflammatory-dystrophic lesion of the denture-bearing oral mucosa characterized by acanthosis, parakeratosis, epithelial atrophy, basal cell degeneration, chronic lymphoplasmacytic inflammation, vascular congestion, and connective tissue fibrosis.



Figure 3. Histopathological features of a chronic inflammatory-dystrophic lesion of the denture-bearing oral mucosa demonstrating acanthosis, parakeratosis, focal epithelial atrophy, chronic inflammatory infiltration, vascular congestion, and stromal fibrosis (H&E stain, original magnification $\times 100$).

Treatment

A comprehensive multidisciplinary treatment approach was implemented. Temporary reduction of denture-wearing time was recommended during the acute inflammatory phase. Professional cleaning and disinfection of the prosthesis were performed, followed by adjustment of traumatic denture borders and correction of occlusal discrepancies.

Topical antiseptic and anti-inflammatory therapy was prescribed to reduce mucosal inflammation. Salivary substitutes and moisturizing oral gels were recommended for management of xerostomia. Detailed instructions regarding denture hygiene and oral self-care were provided. Continued follow-up by both dental and oncology specialists was advised.

Clinical Outcome

At the six-week follow-up examination, substantial clinical improvement was observed. Mucosal erythema and edema had markedly decreased, oral comfort had improved, and the patient reported significant reduction in burning sensation and pain. Denture tolerance improved considerably following prosthetic adjustment and implementation of preventive measures.

Clinical Implications

The findings observed in this representative case reflect the broader pattern of clinical and histopathological alterations identified throughout the study cohort. Women with cervical cancer who use removable dentures may be particularly susceptible to chronic inflammatory and dystrophic changes of the denture-bearing mucosa due to the combined effects of prosthetic irritation, xerostomia,

impaired tissue regeneration, and cancer-related immune dysfunction.

Regular dental examinations, meticulous denture hygiene, timely correction of prosthetic deficiencies, and early investigation of persistent mucosal lesions are essential for preventing complications and improving long-term oral health outcomes in this patient population. Close interdisciplinary collaboration among prosthodontists, oral medicine specialists, pathologists, and oncologists remains crucial for comprehensive patient management.

DISCUSSION

The present retrospective case series evaluated clinical, cytological, and histopathological alterations of denture-bearing oral mucosa in women with cervical cancer using removable dentures. The findings demonstrated a consistent pattern of chronic inflammatory and dystrophic changes, accompanied by vascular alterations and epithelial degeneration. These results suggest a multifactorial pathogenesis involving systemic oncological status, anticancer therapy, salivary dysfunction, immune dysregulation, and chronic mechanical irritation from prosthetic appliances.

The oral mucosa represents a highly responsive tissue characterized by rapid epithelial turnover and close interaction with the immune system and oral microbiota. Consequently, it is particularly vulnerable to systemic diseases and oncological treatments. Chemotherapy and radiotherapy are well documented to induce a spectrum of oral complications, including mucositis, xerostomia, opportunistic infections, and chronic inflammatory lesions, primarily through impaired epithelial regeneration and disrupted immune homeostasis^{13–19,25–27,41}. The present findings are consistent with these previously reported mechanisms.

Xerostomia and salivary dysfunction emerged as key clinical features in the study population. Saliva is essential for maintaining mucosal integrity through lubrication, antimicrobial activity, and facilitation of tissue repair. Its reduction leads to increased frictional trauma, impaired denture retention, and heightened susceptibility to chronic inflammation and denture-related lesions^{28–33}. The high prevalence of erythema, edema, and epithelial atrophy in this cohort underscores the central role of salivary hypofunction in mucosal pathology.

Cytological analysis revealed degenerative epithelial changes, inflammatory infiltration, and disturbances in keratinization without evidence of dysplasia or malignancy. These findings indicate persistent epithelial stress and regenerative impairment. Importantly, the absence of cytological atypia supports the non-neoplastic nature of the observed lesions, although chronic

inflammatory conditions may clinically mimic premalignant changes in medically compromised patients^{24,37}. Cytology may therefore serve as a useful adjunct in long-term monitoring of oral lesions in oncology patients with prosthetic rehabilitation.

Histopathological examination confirmed chronic inflammatory-dystrophic remodeling characterized by acanthosis, parakeratosis, lymphoplasmacytic infiltration, vascular congestion, and connective tissue fibrosis. These features are consistent with denture-associated stomatitis; however, the additional presence of epithelial atrophy and basal cell degeneration suggests a more complex tissue response beyond localized mechanical irritation^{34–36}. This likely reflects systemic treatment-related toxicity and impaired mucosal repair capacity.

Vascular alterations, including congestion and microcirculatory disturbances, may further contribute to tissue hypoxia and delayed healing. Endothelial dysfunction induced by cancer therapy can significantly compromise mucosal resilience and perpetuate chronic inflammatory changes (25,38,40). In parallel, immune dysregulation associated with malignancy and anticancer treatment may enhance cytokine-mediated tissue injury and sustain chronic lymphoplasmacytic infiltration^{12,24–27}.

Alterations in the oral microbiome may also play an important role. Cancer therapy-induced dysbiosis, combined with denture biofilm accumulation and reduced salivary clearance, may promote opportunistic microbial colonization and amplify inflammatory responses^{22,33,43}. These interacting factors likely contribute to the persistence and severity of mucosal lesions observed in this cohort.

Compared with denture-related mucosal changes in otherwise healthy individuals, the lesions observed in this study appear more extensive and multifactorial, suggesting that systemic oncological conditions amplify local prosthetic effects and exacerbate tissue damage.

From a clinical perspective, these findings highlight the importance of regular oral examination in denture-wearing women undergoing treatment for cervical cancer. Preventive strategies, including optimization of denture hygiene, management of xerostomia, early detection of mucosal changes, and multidisciplinary collaboration, are essential to minimize complications and improve quality of life^{26,44}.

LIMITATIONS

This study has several limitations. Its retrospective design limits causal inference regarding the relationship between cervical cancer, its treatment, and oral mucosal changes. The relatively small sample size and absence of a control group restrict generalizability. Additionally, heterogeneity in cancer stage, treatment regimens, and duration of denture use may have influenced the findings. The lack of immunohistochemical and molecular analyses further limits mechanistic interpretation. Nevertheless, the combined clinical, cytological, and histopathological assessment provides valuable insight into denture-associated mucosal alterations in this patient population.

CONCLUSION

Women with cervical cancer wearing removable dentures demonstrate a consistent pattern of inflammatory, vascular, and dystrophic changes in the denture-bearing oral mucosa. These alterations are likely driven by a combination of mechanical trauma, salivary dysfunction, treatment-related tissue injury, immune dysregulation, and microvascular impairment.

Histopathological findings, including acanthosis, parakeratosis, chronic inflammatory infiltration, vascular congestion, and connective tissue fibrosis, support the presence of a chronic inflammatory-dystrophic process rather than isolated mechanical irritation.

These results emphasize the need for systematic oral monitoring, timely prosthetic adjustment, and interdisciplinary management involving prosthodontists, oral medicine specialists, pathologists, and oncologists. Future prospective studies with larger cohorts and molecular-level investigations are warranted to further elucidate the underlying mechanisms and improve preventive and therapeutic approaches.

DECLARATIONS

Conflict of Interest

The author declare no conflict of interest.

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Ethical Approval

Informed consent was obtained from patients. Clinical case approved in accordance with ethical standards.

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REVIEW ARTICLE

THE USE OF PLANT POLYPHENOLS IN THE TREATMENT OF ORAL LICHEN PLANUS: A NARRATIVE REVIEW

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Oral lichen planus (OLP) is a chronic inflammatory disorder of the oral mucosa mediated by T-cell immune responses and recognized by the World Health Organization as a potentially malignant condition. The disease often causes persistent pain, burning sensations, and discomfort during eating and speaking, which can markedly reduce patients' quality of life. Although topical and systemic corticosteroids remain the cornerstone of treatment, their prolonged use may result in local and systemic adverse effects, prompting interest in safer and more sustainable therapeutic approaches.

This narrative review examines the available evidence on the use of plant-derived polyphenols in the management of OLP. Relevant publications published between 2010 and 2026 were identified through searches of PubMed, Scopus, and e-LIBRARY using combinations of the terms "oral lichen planus," "polyphenols," "antioxidants," and "treatment." Clinical studies, systematic reviews, and meta-analyses evaluating topical or systemic plant-based interventions were considered. A growing body of research indicates that several polyphenol-rich natural products, including curcumin, pomegranate extracts, green tea catechins, chamomile, Aloe vera, and Ocimum sanctum (Tulsi), may provide clinical benefits in patients with OLP. Their therapeutic effects are largely attributed to antioxidant, anti-inflammatory, immunomodulatory, and tissue-healing activities. Among the investigated agents, curcumin and Aloe vera have been studied most extensively and have shown results comparable to topical corticosteroids in a number of clinical trials. Nevertheless, differences in study design, treatment protocols, dosage forms, sample sizes, and follow-up periods make direct comparisons difficult and limit the strength of current conclusions. Overall, plant-derived polyphenols appear to be promising adjunctive therapies for oral lichen planus and may offer useful alternatives for selected patients. However, the existing evidence is not yet sufficient to support their routine use as first-line treatment. Further well-designed randomized controlled trials with standardized formulations and longer follow-up periods are needed to better define their efficacy, safety, and place in clinical practice.

Keywords: oral lichen planus; polyphenols; phytotherapy; antioxidants; oral mucosa; curcumin.

INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa characterized by an immune-mediated reaction directed against epithelial basal cells. Although the oral cavity is the most frequently affected

site, lesions may also occur on the skin and genital mucosa. The condition is relatively common, with reported prevalence rates ranging from 0.1% to 4% worldwide, and is observed predominantly in middle-aged and older adults, particularly women ^{1,2}. In some

patients, oral lesions may be accompanied by extraoral manifestations involving the skin or genital mucous membranes, reflecting the systemic nature of the disease process³. The clinical importance of OLP extends beyond its chronic and often symptomatic course. The World Health Organization currently recognizes oral lichen planus as a potentially malignant oral disorder because of its documented, albeit relatively low, risk of progression to oral squamous cell carcinoma⁴. For this reason, affected patients require not only appropriate treatment but also long-term clinical follow-up and careful surveillance. Oral lichen planus presents in several clinical forms, including reticular, plaque-like, atrophic, erosive, and bullous variants⁵. The reticular form is the most common and is usually identified by the presence of characteristic white interlacing striae, known as Wickham's striae. In contrast, erosive and atrophic lesions are frequently associated with pain, burning sensations, sensitivity to spicy foods, and difficulties with eating and speaking, often resulting in a considerable decline in quality of life⁶. Despite decades of investigation, the exact mechanisms responsible for the development of OLP have not been fully clarified. Current evidence indicates that cellular immune dysfunction plays a central role in disease pathogenesis. Cytotoxic T lymphocytes are believed to trigger apoptosis of basal keratinocytes, leading to chronic inflammation and tissue damage within the oral epithelium⁷. In recent years, increasing attention has been paid to the role of oxidative stress as an additional factor contributing to disease initiation and progression^{8,9}. Oxidative stress develops when the production of reactive oxygen and nitrogen species exceeds the capacity of endogenous antioxidant defense systems, resulting in cellular injury and disruption of normal tissue homeostasis¹⁰. Several studies have demonstrated elevated levels of oxidative stress biomarkers together with reduced antioxidant capacity in both saliva and serum samples obtained from patients with OLP¹¹⁻¹⁴. Furthermore, inflammatory cell infiltration within oral lesions may promote excessive generation of reactive oxygen species, thereby sustaining tissue injury and perpetuating chronic inflammation¹³. In a systematic review and meta-analysis, Wang et al. confirmed that patients with OLP consistently exhibit increased oxidative stress and impaired antioxidant defenses, supporting the hypothesis that oxidative imbalance is involved in disease pathogenesis¹⁴. These observations have stimulated interest in therapeutic approaches aimed at restoring redox balance and reducing oxidative tissue damage. Current management of OLP is focused primarily on controlling symptoms, reducing inflammation, promoting healing of oral lesions, and improving patient comfort. Topical corticosteroids remain the treatment of choice for symptomatic disease

and continue to be regarded as the clinical gold standard¹⁵⁻¹⁷. However, long-term corticosteroid therapy may be associated with several adverse effects, including oral candidiasis, mucosal thinning, xerostomia, and, in some cases, systemic complications. As a result, there is growing interest in identifying safer treatment options that can be used for prolonged periods without compromising efficacy. Natural products have attracted increasing attention in recent years as potential adjuncts or alternatives to conventional therapies. Among these, plant-derived polyphenols are of particular interest because they possess a broad range of biological activities, including antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, and tissue-repair properties^{18,19}. These naturally occurring compounds are abundant in fruits, vegetables, medicinal herbs, tea, and many other plant sources. Their ability to modulate inflammatory pathways and neutralize reactive oxygen species provides a strong biological rationale for their use in chronic inflammatory disorders such as OLP. A variety of polyphenol-rich preparations, including curcumin, pomegranate extracts, green tea catechins, chamomile, Aloe vera, and Ocimum sanctum (Tulsi), have been evaluated in clinical studies involving patients with oral lichen planus. Although many of these investigations have reported improvements in symptoms and clinical lesion severity, the available evidence remains heterogeneous, and definitive conclusions regarding their therapeutic value have not yet been established. Therefore, the purpose of this narrative review is to provide an updated overview of the current evidence regarding the use of plant-derived polyphenols in the management of oral lichen planus, with particular emphasis on their biological mechanisms of action, clinical effectiveness, safety profiles, and potential role as adjunctive or alternative therapeutic agents.

MATERIALS AND METHODS

This narrative review was conducted to evaluate the current evidence regarding the use of plant-derived polyphenols in the treatment of oral lichen planus (OLP). A comprehensive literature search was performed using the electronic databases PubMed, Scopus, and eLIBRARY. Publications published between January 2010 and January 2026 were considered eligible for inclusion. The search strategy combined the following keywords and Medical Subject Headings (MeSH) terms: "oral lichen planus," "oral mucosa," "polyphenols," "antioxidants," "phytotherapy," "herbal medicine," "curcumin," "Aloe vera," "green tea," "pomegranate," "chamomile," "Ocimum sanctum," and "treatment."

The inclusion criteria were as follows:

1. Original clinical studies, randomized controlled trials, observational studies, systematic reviews, and meta-

analyses;

2. Studies investigating topical or systemic administration of plant-derived products containing polyphenolic compounds;
3. Studies evaluating clinical outcomes in patients diagnosed with oral lichen planus;

The exclusion criteria included:

1. Animal studies and in vitro investigations;
2. Case reports and conference abstracts without sufficient clinical data;
3. Studies focusing on cutaneous lichen planus without oral involvement;
4. Publications lacking relevant clinical outcome measures;

Titles and abstracts retrieved from the databases were independently screened for relevance. Full-text articles meeting the inclusion criteria were subsequently evaluated. Particular attention was given to study design, sample size, intervention characteristics, duration of treatment, clinical outcomes, safety profile, and reported adverse effects. The selected studies were analyzed descriptively due to substantial heterogeneity in study design, treatment protocols, dosage regimens, outcome assessment methods, and follow-up periods. Therefore, a quantitative meta-analysis was not performed. The available evidence was synthesized narratively, focusing on the mechanisms of action, therapeutic efficacy, safety, and clinical applicability of plant-derived polyphenols in the management of oral lichen planus. The review specifically examined the evidence regarding curcumin, pomegranate (*Punica granatum*) extracts, green tea catechins, chamomile (*Matricaria chamomilla*), Aloe vera, and *Ocimum sanctum* (Tulsi), as these agents were the most frequently investigated plant-derived products in the identified literature.

RESULTS

The reviewed literature demonstrates growing interest in plant-derived polyphenols as adjunctive therapeutic agents for oral lichen planus. Although the quality of evidence varies considerably among studies, most investigations reported improvements in clinical symptoms, lesion severity, or patient-reported outcomes following treatment with polyphenol-rich preparations. Among all investigated compounds, curcumin has received the greatest scientific attention. Multiple randomized clinical trials, systematic reviews, and meta-analyses have consistently shown reductions in pain, burning sensation, and lesion severity in patients treated with topical or systemic curcumin preparations. Several studies reported outcomes comparable to those achieved with topical corticosteroids, while adverse effects were generally mild and infrequent.

Pomegranate-derived preparations have also produced encouraging clinical results. Topical formulations prepared from pomegranate peel or seed extracts were associated with improvements in symptomatic lesions and oral health-related quality of life. In some comparative studies, the clinical response was similar to that observed with topical corticosteroid therapy, suggesting potential value as an adjunctive treatment option. Evidence regarding green tea polyphenols remains more limited. Available studies indicate that catechins, particularly epigallocatechin-3-gallate (EGCG), may reduce oxidative stress and inflammatory activity within oral lesions. Preliminary clinical findings suggest improvement in symptoms and lesion characteristics; however, the small number of controlled studies prevents definitive conclusions regarding efficacy. Chamomile-based preparations have demonstrated beneficial anti-inflammatory effects in patients with symptomatic OLP. Although corticosteroids generally produced a more rapid response during the initial phase of treatment, some studies reported comparable clinical outcomes after several weeks of therapy. These findings suggest that chamomile may be useful in patients seeking non-steroidal treatment approaches. Aloe vera represents one of the most extensively studied herbal interventions for OLP. Clinical trials and systematic reviews have reported significant reductions in pain and lesion severity together with improved mucosal healing. Importantly, several investigations found therapeutic results comparable to those obtained with topical corticosteroids, while treatment-related adverse events were uncommon. Fewer studies have evaluated *Ocimum sanctum* (Tulsi) and other Ayurvedic formulations. Available data indicate potential benefits in reducing pain, burning sensation, and lesion severity; however, the evidence base remains relatively small. Comparative studies suggest that clinical improvements may be less pronounced than those observed with curcumin, although beneficial effects have nevertheless been reported. Despite these promising findings, several limitations were identified across the reviewed literature. Many studies involved small sample sizes, short follow-up periods, and considerable variation in formulations, dosage regimens, and outcome assessment methods. Such heterogeneity makes direct comparison between studies difficult and limits the strength of current recommendations. Overall, the strongest clinical evidence currently supports the use of curcumin and Aloe vera, whereas pomegranate extracts, chamomile, green tea polyphenols, and Tulsi appear promising but require further investigation in larger, well-designed randomized controlled trials. **Table 1** summarizes the principal plant-derived polyphenols, their proposed mechanisms of action, and reported clinical effects.

Table 1. Biological Activities and Reported Clinical Effects of Plant-Derived Polyphenols Used in the Management of Oral Lichen Planus

Plant-derived agent	Major bioactive compounds	Proposed mechanisms of action	Reported clinical effects	Key references
Curcumin (<i>Curcuma longa</i>)	Curcuminoids	Inhibition of NF-κB signaling, suppression of pro-inflammatory cytokines, antioxidant activity, and immunomodulation	Reduction in pain scores, burning sensation, and clinical lesion severity; improvement in overall clinical outcomes	[23–27]
Pomegranate (<i>Punica granatum</i>)	Ellagitannins, punicalagins, flavonoids	Antioxidant activity, modulation of inflammatory pathways, and promotion of tissue repair	Improvement in lesion healing, symptom severity, and oral health-related quality of life	[29–31]
Greentea (<i>Camellia sinensis</i>)	Catechins, particularly epigallocatechin-3-gallate (EGCG)	Free radical scavenging, anti-inflammatory activity, and inhibition of oxidative cellular damage	Reduction in symptom intensity and improvement in clinical lesion characteristics	[34–36]
Chamomile (<i>Matricaria chamomilla</i>)	Flavonoids, terpenoids, coumarins	Anti-inflammatory, antioxidant, antimicrobial, and soothing effects	Reduction in pain, erythema, and inflammatory manifestations	[39–41]
Aloe vera	Polyphenols, vitamins, sterols, polysaccharides	Anti-inflammatory and antioxidant activity; stimulation of epithelial regeneration and wound healing	Enhanced mucosal healing and reduction in pain and discomfort	[44–48]
Ocimum sanctum (Tulsi)	Eugenol, rosmarinic acid, flavonoids	Antioxidant and immunomodulatory effects; inhibition of inflammatory mediators	Reduction in pain and burning sensation with improvement in overall clinical symptoms	[49,50]

Table 2 presents the available clinical evidence, treatment protocols, and levels of evidence for the investigated interventions.

Table 2. Comparative Clinical Characteristics of Plant-Derived Preparations Used in Oral Lichen Planus

Intervention	Pharmaceutical form	Dosage and treatment regimen	Comparison with conventional therapy
Curcumin (<i>Curcuma longa</i>)	Gel, mucoadhesive paste, oral capsules	Topical concentrations ranging from 1–5%, applied 2–6 times daily; oral administration up to 80 mg/day	Therapeutic efficacy comparable to topical corticosteroids in several clinical studies [23–27]
Pomegranate (<i>Punica granatum</i>)	Topical gel	Applied 4–5 times daily for 4 weeks	Clinical outcomes comparable to topical triamcinolone acetonide [29–31]
Green tea (<i>Camellia sinensis</i>)	Oral tablets, buccal formulations	300–450 mg/day	Limited clinical evidence; further controlled studies are required [34–

Intervention	Pharmaceutical form	Dosage and treatment regimen	Comparison with conventional therapy
Chamomile (<i>Matricaria chamomilla</i>)	Gel, topical cream	2% formulation applied for approximately 4 weeks	36] Clinical efficacy comparable to corticosteroid therapy after 4 weeks of treatment [38–41]
Aloe vera	Topical gel	Preparations containing up to 97% <i>Aloe vera</i> extract	Clinical effectiveness comparable to topical corticosteroids with a favorable safety profile [44–48]
Polyherbal Ayurvedic formulation	Topical gel	Applied for approximately 10 days	Demonstrated superior outcomes compared with placebo [49]
Tulsi (<i>Ocimum sanctum</i>)	Topical ointment	Applied twice daily for up to 3 months	Clinical improvement observed, although efficacy appeared lower than that of curcumin in comparative studies [50]

DISCUSSION

Oral lichen planus (OLP) is a chronic immune-mediated inflammatory disorder with a well-recognized potential for malignant transformation and therefore often requires long-term clinical management ^{1,3,4,6}. In recent years, increasing attention has been directed toward plant-derived polyphenols as potential therapeutic agents due to their anti-inflammatory, antioxidant, immunomodulatory, and tissue-regenerative properties ^{18,47}. These bioactive compounds may target multiple pathogenic pathways involved in OLP while simultaneously reducing the adverse effects commonly associated with conventional pharmacotherapy. A growing body of evidence indicates that oxidative stress plays a central role in the pathogenesis of OLP. Patients with OLP frequently demonstrate elevated levels of reactive oxygen species (ROS) alongside a reduction in endogenous antioxidant defense mechanisms, which collectively contribute to epithelial damage, persistent inflammation, and disease progression ^{8,11,14}. Accordingly, therapeutic strategies aimed at modulating oxidative stress appear to be a rational and promising approach. Within this context, plant-derived polyphenols are particularly noteworthy due to their ability to neutralize free radicals, regulate inflammatory signaling pathways, and promote tissue repair. Among the various natural compounds investigated, curcumin has received the most extensive scientific attention. Clinical studies and systematic reviews have reported that both topical and systemic formulations of curcumin can significantly reduce pain intensity, burning sensation, and lesion severity in patients with OLP ^{20,21,26}.

In several studies, curcumin demonstrated clinical efficacy comparable to that of corticosteroids, particularly during longer follow-up periods ^{23,27}. The therapeutic effects of curcumin are mainly attributed to its inhibitory action on pro-inflammatory mediators, including cyclooxygenase and lipoxygenase pathways, as well as its ability to modulate cytokine expression and inflammatory cascades ²². These findings suggest that curcumin may represent a valuable adjunctive or even alternative therapeutic option, especially in patients who are intolerant to corticosteroid therapy or require prolonged treatment.

Pomegranate (*Punica granatum*)-derived preparations have also shown promising therapeutic potential.

Clinical investigations have demonstrated that topical gels containing pomegranate seed or peel extracts can lead to significant improvement in symptoms and overall quality of life in patients with OLP ^{29,30}.

The beneficial effects of pomegranate are primarily attributed to its high concentration of polyphenolic compounds, particularly flavonoids and tannins, which possess strong antioxidant and anti-inflammatory properties²⁸. Importantly, several studies have reported outcomes comparable to those achieved with topical corticosteroids such as triamcinolone, supporting its possible role in clinical practice.

Green tea polyphenols, especially epigallocatechin gallate (EGCG), have also attracted considerable attention due to their potent antioxidant, anti-inflammatory, and anticarcinogenic properties^{32,34}. Preliminary clinical studies have reported reductions in lesion size and symptom severity following green tea-based interventions. However, the current evidence remains limited due to small sample sizes, short observation periods, and methodological heterogeneity. Additionally, the low bioavailability of EGCG represents a significant limitation for its clinical application³³. Therefore, further well-designed clinical trials are necessary to clarify its therapeutic efficacy and optimal delivery systems in OLP management.

Chamomile has long been used in traditional medicine for inflammatory oral conditions due to its anti-inflammatory, antimicrobial, and antioxidant properties. Clinical studies have demonstrated that chamomile-based preparations can reduce pain and improve clinical symptoms in patients with OLP^{37,39,41}. Although corticosteroids may provide faster symptomatic relief in the early stages of treatment, several studies have reported comparable long-term outcomes between chamomile and corticosteroid therapy. These findings suggest that chamomile may serve as a safe complementary therapeutic option for selected patients.

Aloe vera is another extensively studied natural agent with well-documented anti-inflammatory, antioxidant, antimicrobial, and wound-healing effects. Clinical trials and systematic reviews have shown significant improvements in pain, lesion size, and overall clinical appearance in patients treated with Aloe vera preparations^{44,45,46}. Notably, several studies have reported that its effectiveness may be comparable to topical corticosteroids while offering a more favorable safety profile⁴⁸. This makes Aloe vera an attractive option for long-term management of chronic OLP. In addition, recent research has explored the therapeutic potential of combined herbal formulations. Ayurvedic preparations containing turmeric, calendula, and Tulsi have demonstrated superior outcomes compared with placebo in patients with erosive OLP⁴⁹. Tulsi (*Ocimum sanctum*) itself possesses strong antioxidant and immunomodulatory properties that may contribute to

symptom improvement. Nevertheless, comparative studies suggest that turmeric-based formulations may provide greater reductions in pain and burning sensation than Tulsi alone⁵⁰.

Overall, the evidence reviewed in this study indicates that several plant-derived polyphenols exhibit therapeutic efficacy that may approach that of conventional corticosteroid therapy in the management of OLP symptoms. Their favorable safety profiles, lower incidence of adverse effects, and potential affordability make them attractive adjunctive or alternative options to standard treatment. However, the current literature is characterized by substantial heterogeneity in study design, sample size, treatment duration, formulation types, and outcome assessment methods, which limits direct comparison across studies and prevents definitive clinical recommendations^{19,43}.

Future research should focus on large-scale, multicenter randomized controlled trials with standardized protocols, longer follow-up periods, and uniform outcome measures. Particular attention should be given to optimal dosing strategies, delivery systems, treatment duration, and pharmacodynamic mechanisms. Moreover, further studies are needed to explore whether plant-derived polyphenols may play a role in preventing malignant transformation of OLP lesions, which remains a critical clinical concern⁴.

Overall, plant-derived polyphenols represent a promising and biologically plausible therapeutic approach for OLP. While they cannot yet replace conventional therapies, they may serve as effective adjunctive or alternative options, particularly in patients requiring long-term management or those experiencing adverse effects from corticosteroid therapy.

CONCLUSION

Current evidence suggests that plant-derived polyphenols possess significant anti-inflammatory, antioxidant, immunomodulatory, and regenerative properties that may be beneficial in the management of oral lichen planus. Natural compounds such as curcumin, Aloe vera, pomegranate extracts, chamomile, green tea catechins, and Tulsi have demonstrated encouraging clinical outcomes, including reductions in pain intensity, burning sensation, lesion severity, and overall improvement in patients' quality of life^{23,30,44,49}. Among the investigated agents, curcumin and Aloe vera currently have the strongest clinical evidence base. Both have demonstrated therapeutic efficacy comparable to topical corticosteroids in multiple studies while potentially offering a superior safety profile^{23,45}.

Nevertheless, the overall evidence remains limited due to small sample sizes, variability in study designs, heterogeneity in formulations and dosing regimens, and insufficient long-term follow-up data. Therefore, plant-derived polyphenols should currently be considered promising adjunctive or complementary therapeutic approaches rather than definitive replacements for conventional corticosteroid-based therapy. Well-designed multicenter randomized controlled trials with standardized methodologies are essential to determine optimal formulations, dosing regimens, long-term safety, and their potential role in preventing disease progression and malignant transformation in oral lichen planus.

DECLARATIONS

Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

Conflict of Interest

The author declare no conflict of interest.

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REVIEW ARTICLE

**ETIOLOGICAL ASPECTS AND EPIDEMIOLOGICAL PATTERNS OF KERATOACANTHOMA:
NARRATIVE REVIEW**

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ABSTRACT

Keratoacanthoma (KA) is a rapidly developing keratinizing epithelial neoplasm whose classification remains controversial because of its close relationship to cutaneous squamous cell carcinoma (cSCC). Despite its frequent occurrence in dermatological practice, the epidemiology and pathogenesis of KA remain incompletely understood. This narrative review summarizes current evidence regarding the etiological factors and epidemiological characteristics of KA. Available data indicate marked geographic variation in incidence, largely reflecting differences in ultraviolet (UV) exposure, environmental conditions, and population skin phototypes. The tumor occurs predominantly in fair-skinned individuals and is most commonly diagnosed in older adults with a history of chronic sun exposure.

Current evidence supports a multifactorial origin of KA. Ultraviolet radiation is considered the principal environmental risk factor and is associated with characteristic molecular alterations, including mutations in TP53 and HRAS. Additional contributors include human papillomavirus infection, particularly cutaneous beta-papillomavirus types; immunological dysregulation related to immunosuppressive therapy and immune-modulating drugs; chronic inflammatory stimuli following trauma, surgical procedures, or tattooing; exposure to chemical carcinogens such as arsenic and tar-derived compounds; and inherited cancer-predisposition syndromes, including Muir–Torre and Ferguson–Smith syndromes. Increasing evidence suggests that interactions between genetic susceptibility, environmental exposures, and local immune responses play a central role in tumor development. In conclusion, keratoacanthoma represents a multifactorial neoplastic process arising from the combined effects of environmental, genetic, viral, and immunological factors. Further epidemiological and molecular studies are needed to clarify disease mechanisms and improve risk stratification.

Keywords: keratoacanthoma, etiology of keratoacanthoma, epidemiology of keratoacanthoma.

INTRODUCTION

Keratoacanthoma (KA) is a distinctive keratinizing epithelial neoplasm of the skin characterized by rapid growth, a typical crateriform architecture, and a variable biological behavior. It most frequently occurs on chronically sun-exposed areas, particularly in elderly

patients, and usually presents as a rapidly developing dome-shaped lesion with a central keratin-filled depression. The clinical appearance of KA often resembles cutaneous squamous cell carcinoma (cSCC), creating significant diagnostic difficulties in daily dermatological and histopathological practice.

Although KA has historically been described as a lesion capable of spontaneous regression, its potential relationship with cSCC remains one of the most debated issues in cutaneous oncology¹⁻³.

For many years, KA was considered a separate benign or borderline epithelial proliferation with a characteristic evolution consisting of rapid enlargement, stabilization, and possible involution. However, increasing evidence from morphological, immunohistochemical, and molecular studies has demonstrated substantial similarities between KA and well-differentiated cSCC. These similarities include overlapping histological features, common genetic alterations, and comparable responses to environmental carcinogenic factors. As a result, the previous concept of KA as an entirely independent benign lesion has gradually changed, and its classification has become a subject of continuous discussion among dermatologists, pathologists, and oncologists^{1,3,24}.

A major turning point in the understanding of KA occurred with the publication of the fourth edition of the World Health Organization (WHO) Classification of Skin Tumours in 2018. Based on accumulated clinical, histopathological, and molecular data indicating a close biological relationship between KA and cSCC, KA was incorporated into the spectrum of well-differentiated cutaneous squamous cell carcinomas and categorized as keratoacanthoma-type squamous cell carcinoma. This approach reflects the current view that KA and cSCC may represent different manifestations of closely related keratinocytic neoplastic processes rather than completely distinct diseases. According to the WHO classification, this entity is coded as ICD-O 8071/3 and is represented within ICD-10 and ICD-11 classification systems. Historically, KA has been described by several alternative terms, including molluscum sebaceum, keratinous molluscum, pseudocarcinomatous molluscum, and Gougerot's verruciform epithelioma^{1-3,25}.

The etiology and pathogenesis of KA are considered multifactorial, involving the interaction of genetic susceptibility, environmental influences, and alterations in epidermal homeostasis. Chronic ultraviolet (UV) radiation exposure is regarded as one of the most important contributing factors, particularly due to its ability to induce DNA damage and promote mutations affecting key regulatory pathways involved in keratinocyte proliferation and differentiation. Alterations in tumor suppressor mechanisms, including TP53 dysfunction, as well as changes in oncogenic signaling pathways such as RAS-related pathways,

have been described in KA and may contribute to abnormal keratinocyte growth. In addition, immune dysregulation, impaired local immune surveillance, viral factors, trauma, and exposure to certain chemical agents have been suggested as possible triggers. The interaction of these mechanisms may explain the heterogeneous clinical course of KA, including both spontaneous regression and progression with morphological features resembling cSCC^{12,15-17}.

Despite extensive investigation, the exact biological nature of KA remains incompletely understood. The difficulty in predicting its behavior and the considerable overlap with cSCC continue to make KA an important diagnostic and scientific challenge. Further studies focusing on molecular mechanisms, genetic alterations, and clinicopathological correlations are necessary to better define the relationship between KA and cSCC and to improve the accuracy of diagnosis and classification^{1,3,24}.

The present narrative review aims to summarize and critically discuss current evidence regarding the epidemiology, etiological factors, and biological behavior of keratoacanthoma. Particular attention is given to the environmental, viral, genetic, and immunological mechanisms that may contribute to tumor development and influence its clinical course. The review is based on published clinical, epidemiological, and experimental studies, as well as contemporary international classification systems that have shaped current understanding of this unique and still controversial cutaneous neoplasm.

EPIDEMIOLOGY

Although keratoacanthoma (KA) is considered a relatively common cutaneous neoplasm, its epidemiology remains incompletely characterized [3]. Most of the available evidence originates from single-center studies or retrospective case series involving relatively small patient cohorts, which limits the ability to draw definitive conclusions regarding the global burden of the disease. Consequently, large population-based investigations remain particularly valuable for understanding the incidence and demographic characteristics of KA.

One of the most important epidemiological studies of keratoacanthoma is the Queensland Skin Cancer Cohort (QSkin) study conducted in Queensland, Australia, between 2010 and 2014^{7,8}. This prospective population-based cohort study provided the first large-scale assessment of KA incidence and associated risk factors.

The analysis included 40,438 individuals aged 40–69 years selected from a random sample of 193,344 Queensland residents. Among these participants, 584 patients were diagnosed with keratoacanthoma.

The findings demonstrated an age-standardized incidence rate of 409 cases per 100,000 person-years based on the Australian standard population. Men were affected slightly more frequently than women, accounting for 58% of all diagnosed cases. The majority of patients were aged 60 years or older (76%), while fair-skinned individuals represented approximately 80% of the affected population. Notably, a history of actinic keratosis or cutaneous squamous cell carcinoma was documented in 89% of patients, emphasizing the close epidemiological relationship between these lesions and chronic ultraviolet-induced skin damage ^{7,8}.

The study also provided valuable information regarding lesion distribution. Keratoacanthomas were most commonly located on the lower extremities, including the legs and feet (48%), whereas involvement of the head and neck region was relatively uncommon (7%). An additional noteworthy observation was the occurrence of multiple lesions. Although 584 patients were included in the analysis, a total of 738 keratoacanthomas were diagnosed, indicating that approximately 18% of affected individuals developed multiple tumors ⁸.

Earlier population-based data were obtained from a five-year epidemiological study conducted on the island of Kauai, Hawaii, between 1983 and 1987 ^{9,10}. During this period, 53 incident cases of keratoacanthoma were identified, including 36 men and 17 women. The average annual incidence was calculated at 106 cases per 100,000 inhabitants. Interestingly, the incidence of keratoacanthoma was found to be comparable to that of cutaneous squamous cell carcinoma, challenging the previously accepted assumption that KA occurred approximately three times less frequently than cSCC. Subsequent investigations performed in different geographic regions demonstrated substantial variability in the KA-to-cSCC ratio, ranging from 1:0.6 to 1:5, suggesting that environmental and population-specific factors may significantly influence disease occurrence ^{9–11}.

The Hawaiian study further demonstrated that the hands and shoulders were the most common anatomical sites affected by keratoacanthoma, whereas lesions of the trunk and other body regions occurred less frequently. The investigators also observed a lower incidence

among individuals with darker skin pigmentation, supporting the widely accepted view that KA occurs most frequently in individuals with Fitzpatrick skin phototypes I–III. Men were affected approximately twice as often as women, with a male-to-female ratio of 2:1 ^{9–11}.

Although keratoacanthoma has been reported across virtually all age groups, its incidence increases steadily with advancing age. The highest incidence rates are observed in individuals aged 70 years and older, whereas the disease is distinctly uncommon in patients younger than 20 years of age ^{2,9,11}.

Taken together, currently available epidemiological evidence indicates that keratoacanthoma predominantly affects fair-skinned older adults, particularly men, and occurs most frequently in populations exposed to high levels of ultraviolet radiation. Nevertheless, significant geographic variation exists, reflecting differences in environmental exposure, genetic susceptibility, skin phototype distribution, and diagnostic practices. Additional large-scale population studies are required to better define the global epidemiological patterns of this unique and still controversial cutaneous neoplasm.

Table 1. Epidemiological characteristics of keratoacanthoma

Parameter	Current evidence
Typical age group	Older adults (>60–70 years)
Sex predominance	Male predominance
Skin type	Fitzpatrick I–III
Main environmental factor	Chronic UV exposure
Common locations	Sun-exposed skin, extremities
Multiple lesions	Reported in a subset of patients
Association	Actinic keratosis and cSCC history

ETIOLOGY

Despite decades of research, no single unifying hypothesis has been established to explain the etiology and pathogenesis of keratoacanthoma (KA). The tumor is generally believed to originate from the hair follicle epithelium, while its development appears to result from the interaction of multiple environmental, genetic,

viral, and immunological factors. Among the most frequently implicated risk factors are chronic ultraviolet (UV) radiation exposure, chemical carcinogens, immunosuppression, certain medications, genetic susceptibility, human papillomavirus (HPV) infection, and skin trauma or surgical interventions^{2-5,11-14}. Notably, most etiological factors associated with KA closely resemble those recognized for invasive cutaneous squamous cell carcinoma (cSCC).

Ultraviolet Radiation and Photocarcinogenesis

Chronic exposure to ultraviolet radiation is widely considered one of the most important risk factors for keratoacanthoma development. This association is supported by the characteristic distribution of lesions, which occur predominantly on chronically sun-exposed areas of the body, including the face, ears, scalp, and dorsal surfaces of the hands. These anatomical locations account for approximately 80–85% of all reported cases⁶.

The risk of developing KA is particularly elevated among individuals with Fitzpatrick skin phototypes I and II. Numerous studies have demonstrated that cumulative lifetime sun exposure contributes significantly to disease risk regardless of the pattern of exposure, while a history of previous sunburns represents an additional predisposing factor^{2,12}.

At the molecular level, UV-induced skin carcinogenesis is associated with mutations affecting tumor suppressor genes and signaling pathways involved in cellular proliferation and apoptosis. Similar to cutaneous squamous cell carcinoma, keratoacanthomas frequently exhibit alterations involving TP53, HRAS, and other genes that enable damaged keratinocytes to evade programmed cell death and continue proliferating^{12,15,16}.

Human Papillomavirus Infection

Human papillomavirus infection has long been considered a potential contributor to keratoacanthoma development. Particular attention has been focused on HPV types 9, 11, 13, 16, 18, 24, 25, 33, 37, and 57. Nevertheless, despite the growing number of studies demonstrating an association between HPV and KA, the precise role of the virus in tumor initiation and progression remains uncertain^{11,17}.

The hypothesis of viral involvement was first proposed in the 1960s following the identification of virus-like particles within tumor cells using electron microscopy.

Subsequent molecular investigations confirmed the presence of HPV DNA in keratoacanthoma specimens. Current evidence suggests that cutaneous beta-HPV types may be of particular importance in the pathogenesis of the disease^{11,17}.

Interestingly, studies evaluating viral load during different stages of tumor evolution have revealed dynamic changes in HPV DNA concentration. Viral load tends to increase during the growth and stabilization phases of keratoacanthoma but decreases dramatically during spontaneous regression. In some regressing lesions, HPV DNA becomes undetectable altogether, suggesting a possible role for viral infection in tumor maintenance rather than initiation alone^{11,17}.

The potential contribution of viral and immune-mediated mechanisms has also been highlighted by reports of keratoacanthomas developing at sites of COVID-19 vaccination. Both solitary and eruptive forms have been described, with lesions occurring directly within the vaccination area and demonstrating a clear temporal association with vaccine administration^{18,19}.

Drug-Induced Keratoacanthoma and Immunological Factors

The spontaneous development of multiple keratoacanthomas has been reported in association with several pharmacological agents. Among the most frequently implicated medications are targeted therapies used in the treatment of advanced melanoma, particularly inhibitors of the MAPK signaling pathway (RAS–RAF–MEK–ERK). Vemurafenib and sorafenib are the drugs most commonly associated with the development of eruptive keratoacanthomas and non-melanoma skin cancers^{20,21}.

Dabrafenib has also been linked to an increased risk of keratinocytic neoplasms, although the incidence appears to be considerably lower than that observed with vemurafenib (approximately 14% versus 26%)²¹. The underlying mechanism is thought to involve paradoxical activation of proliferative signaling pathways and alterations in immune regulation. Inhibition of PI3K-, MAP kinase-, and NF-κB-related pathways may reduce cytokine release from Langerhans cells and impair T-lymphocyte-mediated surveillance against newly emerging tumor cells^{15,20}. An increased risk of keratoacanthoma has also been reported in patients receiving immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), including pembrolizumab and sintilimab.

Furthermore, cases have been described in individuals undergoing immunosuppressive therapy with leflunomide for active rheumatoid arthritis, further supporting the role of immune dysregulation in tumor development ¹². Skin Trauma and Tattoo-Associated Keratoacanthoma Traumatic injury is recognized as another important triggering factor for keratoacanthoma. Surgical procedures, burns, chronic irritation, and other forms of skin damage have all been associated with subsequent tumor development. In recent years, particular attention has been directed toward keratoacanthomas arising within tattooed skin. A systematic review demonstrated that approximately 79.2% of tattoo-associated keratoacanthomas occurred within red-pigmented areas of tattoos, suggesting a possible role for specific pigment components in tumor induction ^{22,23}.

However, the pathogenesis of tattoo-related KA remains incompletely understood. Current evidence suggests that several mechanisms may contribute simultaneously, including local tissue trauma caused by tattooing, chronic inflammatory responses, ultraviolet radiation exposure, genetic susceptibility, and the biological effects of pigment constituents. The carcinogenic potential of tattoo pigments remains insufficiently investigated, although mercury sulfide, commonly used in red inks, has been proposed as a possible carcinogenic agent. Other substances identified in red tattoo pigments, including iron, zinc, and titanium oxides, have also attracted attention because of their potential biological activity ^{22,23}.

Genetic Predisposition

Several hereditary disorders are associated with an increased risk of keratoacanthoma development, providing evidence for an underlying genetic susceptibility. These include Muir–Torre syndrome, Ferguson–Smith syndrome, Witten and Zak familial multiple keratoacanthoma, xeroderma pigmentosum, and generalized eruptive keratoacanthoma of Grzybowski, among others ^{12,24}. The occurrence of KA within these syndromes supports the concept that inherited abnormalities affecting DNA repair, tumor suppression, or immune regulation may facilitate tumor formation.

Chemical Carcinogens

Long-term exposure to chemical carcinogens has been implicated in the development of both invasive cutaneous squamous cell carcinoma and keratoacanthoma. Potentially hazardous substances

include coal tar, pitch, arsenic, soot, paraffin, tar products, unrefined kerosene, creosote, and mineral oils ^{5,13,25}.

Occupational exposure to such agents has been documented in approximately 42% of patients with keratoacanthoma in some clinical series ²⁵.

Chronic contact with chemical carcinogens promotes cutaneous inflammation, epithelial hyperplasia, cellular atypia, and tissue remodeling. Over time, these alterations may lead to the formation of focal proliferative lesions that can subsequently evolve into malignant epithelial tumors ^{5,13}.

Table 2. Etiological factors and proposed mechanisms in KA development

Risk factor	Proposed mechanism
UV radiation	TP53 mutations, keratinocyte damage
HPV infection	Viral persistence and immune modulation
Immunosuppression	Reduced tumor immune surveillance
MAPK inhibitors	Paradoxical pathway activation
Trauma/tattoos	Chronic inflammation
Genetic syndromes	DNA repair defects
Chemical carcinogens	Chronic epithelial stimulation

Although the exact mechanisms underlying keratoacanthoma development remain incompletely understood, current evidence suggests that several etiological factors may interact through complex molecular pathways. Ultraviolet radiation, genetic alterations, immune disturbances, viral factors, and external triggers may promote abnormal keratinocyte proliferation and contribute to the formation of the characteristic keratoacanthoma lesion.

The balance between proliferative signals and immune-mediated regression may influence the clinical course of keratoacanthoma, including spontaneous regression or progression toward a squamous cell carcinoma-like phenotype (Figure 1).

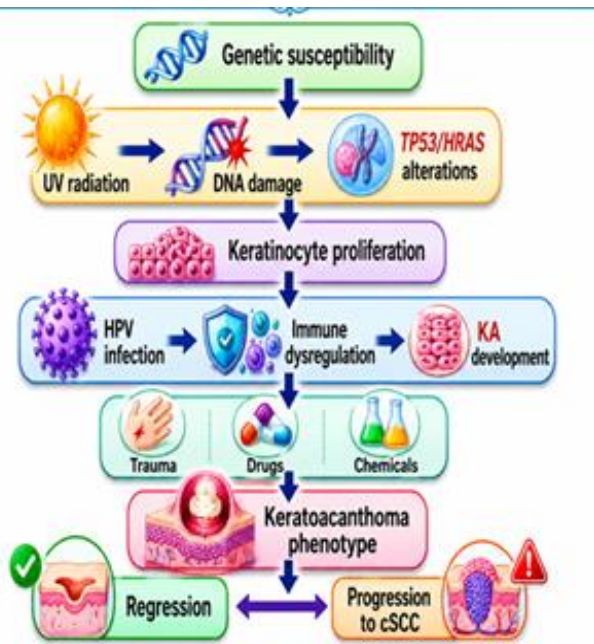


Figure 1. Multifactorial etiological factors and proposed mechanisms involved in keratoacanthoma development.

DISCUSSION

Keratoacanthoma remains one of the most debated entities in dermatopathology because its biological behavior is not yet completely understood. Historically, it was considered a benign, self-limiting epithelial tumor; however, accumulating clinical, histopathological, and molecular data indicate a close biological relationship with cutaneous squamous cell carcinoma. This overlap remains an important challenge in diagnosis and clinical decision-making^{1-3,12}. The findings summarized in this review support the concept that keratoacanthoma is a multifactorial disease resulting from complex interactions between environmental exposures, genetic susceptibility, viral factors, and immune regulation. Chronic ultraviolet radiation appears to play a central role in tumor development, both through cumulative photodamage and through the induction of molecular alterations involving genes such as TP53 and HRAS^{12,15,16}. The predominance of lesions on chronically sun-exposed skin and the increased incidence among fair-skinned individuals further support the importance of ultraviolet radiation in disease pathogenesis⁷⁻¹².

The contribution of human papillomavirus remains controversial. Although HPV DNA has been detected in numerous keratoacanthoma specimens and viral load appears to correlate with certain stages of tumor evolution, current evidence is insufficient to establish a direct causal relationship^{11,17}. Similar uncertainty exists regarding the role of trauma, tattoo pigments, and

vaccine-associated cases, which may represent triggering factors in predisposed individuals rather than independent causes of tumor formation^{18,19,22,23}.

Another important observation is the increasing number of reports describing keratoacanthomas associated with targeted anticancer therapies and immune-modulating agents. These findings suggest that immune surveillance and signaling pathways involved in keratinocyte proliferation may play a critical role in maintaining cutaneous homeostasis. Disruption of these mechanisms may facilitate the emergence of keratoacanthoma in susceptible individuals^{12,20,21}.

Despite significant advances in molecular pathology, a major challenge remains the absence of reliable biomarkers capable of consistently distinguishing keratoacanthoma from invasive cutaneous squamous cell carcinoma. This diagnostic uncertainty continues to influence clinical decision-making and largely explains why complete surgical excision remains the preferred therapeutic approach in most cases¹⁻³.

Overall, the available evidence suggests that keratoacanthoma should not be viewed as a single disease entity with a uniform pathogenesis. Instead, it is more likely to represent a biologically heterogeneous group of lesions sharing common clinical and histopathological features while arising through multiple overlapping pathogenic pathways.

LIMITATIONS AND FUTURE RESEARCH DIRECTIONS

Several limitations should be considered when interpreting the current evidence regarding keratoacanthoma. First, much of the available literature consists of retrospective studies, case series, and isolated case reports, while large prospective investigations remain relatively scarce. Second, significant heterogeneity exists among published studies with respect to diagnostic criteria, patient selection, and classification systems, which complicates direct comparisons between studies. Third, the ongoing debate regarding the biological nature of keratoacanthoma itself may have influenced epidemiological estimates and clinical reporting, particularly in studies conducted before the adoption of contemporary WHO classifications.

Further research is required to clarify the molecular mechanisms underlying keratoacanthoma development,

progression, and spontaneous regression. Particular attention should be directed toward the identification of diagnostic biomarkers capable of reliably differentiating keratoacanthoma from invasive cutaneous squamous cell carcinoma. Additional large-scale epidemiological studies are also needed to better define geographic variations in disease incidence and to evaluate the relative contributions of ultraviolet radiation, viral infection, genetic predisposition, and immune dysregulation. Advances in molecular profiling and translational research may ultimately facilitate more individualized diagnostic and therapeutic approaches for patients with keratoacanthoma.

Table 3. Keratoacanthoma and cutaneous SCC: similarities and differences

Feature	KA	cSCC
Growth	Rapid	Variable
Histology	Similar	Similar
Regression	Possible	Rare
Metastatic risk	Very low	Present

CONCLUSION

Keratoacanthoma is a unique keratinizing epithelial neoplasm characterized by complex and still incompletely understood biological behavior. Current evidence supports a multifactorial pathogenesis involving chronic ultraviolet radiation, genetic alterations, viral factors, immune dysregulation, chemical carcinogens, pharmacological triggers, and traumatic skin injury. Epidemiological studies consistently demonstrate a predominance among fair-skinned older individuals and populations exposed to high levels of solar radiation.

Although keratoacanthoma has traditionally been regarded as a self-limiting lesion, accumulating clinical and molecular evidence indicates that some cases may share biological features with cutaneous squamous cell carcinoma. However, important questions regarding its origin, progression, and potential for regression remain unresolved.

Future investigations focusing on molecular biomarkers, tumor microenvironment interactions, and mechanisms of spontaneous regression may improve diagnostic accuracy and enable more personalized management strategies. A better understanding of these

processes may ultimately reduce diagnostic uncertainty and contribute to more effective treatment approaches for affected patients.

DECLARATIONS

Competing Interests

The authors declare no conflict of interest.

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None.

Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

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REVIEW ARTICLE

**CLINICAL-MORPHOLOGICAL FEATURES AND NEW ASPECTS OF KERATOACANTHOMA
TREATMENT: NARRATIVE REVIEW**

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ABSTRACT

Keratoacanthoma (KA) is a well-differentiated (G1) epithelial tumor characterized by rapid growth, low malignant potential, and a minimal risk of metastasis. The biological behavior of KA remains a subject of scientific debate. The main challenge lies in its significant clinical and histopathological similarity to cutaneous squamous cell carcinoma (cSCC). Clinically, KA is usually easy to recognize because of its characteristic appearance. It presents as a rapidly growing, dome-shaped nodule with a central crater-like depression filled with keratinous material. The tumor typically progresses through three sequential stages—growth, stabilization, and spontaneous regression. The entire cycle usually lasts 3–9 months and often culminates in the formation of an atrophic scar. Histopathological examination remains the only reliable method for distinguishing KA from cSCC. Accurate assessment requires an excisional or deep incisional biopsy, as superficial sampling techniques do not adequately demonstrate the overall architecture of the lesion. The tumor is believed to originate from the hair follicle. The key dermoscopic features shared by both KA and cSCC include white circles, central keratin accumulation, white structureless areas, and linear, branched, hairpin, and glomerular vessels. Because the dermoscopic appearance of KA closely resembles that of cSCC, a definitive diagnosis can only be established by histopathological examination. Current treatment strategies should be individualized according to lesion characteristics, anatomical location, growth pattern, histopathological findings, and patient-related factors. Surgical excision remains the preferred approach when malignancy cannot be excluded or when aggressive clinical features are present. In selected patients, tissue-preserving modalities—including intralesional methotrexate, intralesional 5-fluorouracil, cryotherapy, laser-based techniques, and other conservative approaches—may also be considered. In this narrative review, we summarize the clinical, dermoscopic, and histopathological features of KA and discuss contemporary therapeutic strategies. The analysis is complemented by the authors' clinical experience and dermoscopic observations from routine dermatological practice, highlighting the practical value of dermoscopy in lesion assessment, the selection of representative biopsy sites, and individualized treatment planning.

Keywords: keratoacanthoma; dermoscopy; histopathology; individualized treatment; clinicodermoscopic correlation.

INTRODUCTION

Keratoacanthoma (KA) is a rapidly growing keratinizing epithelial tumor that continues to pose a diagnostic challenge in dermatopathology due to its close clinicopathological overlap with cutaneous squamous cell carcinoma (cSCC)¹⁻³. It typically presents as a dome-shaped nodule with a central keratin-filled crater and develops over a short clinical course. Despite its often characteristic appearance, reliable distinction from invasive cSCC based on clinical features alone remains difficult^{1-3, 9, 10}.

The biological nature of KA remains controversial. It has traditionally been considered a lesion with a triphasic evolution consisting of rapid growth, a plateau phase, and possible spontaneous regression^{2,3,13}. However, this behavior is inconsistent and unpredictable, as a subset of lesions may persist or demonstrate clinically aggressive features^{1,3,21}. Consequently, KA is currently regarded as a keratinizing epithelial neoplasm requiring careful diagnostic assessment rather than a uniformly self-limited process^{1, 2, 5}.

Accurate diagnosis relies on the integration of clinical evaluation, dermoscopy, and histopathological examination. Dermoscopy may provide supportive diagnostic clues by revealing characteristic vascular and keratin-related patterns and may assist in the assessment of crateriform lesions, including KA and cSCC^{18,20}.

Nevertheless, due to substantial histomorphological overlap with well-differentiated cSCC, histopathological examination remains essential for definitive diagnosis and exclusion of malignancy^{1, 2, 18, 21}.

Classification

ICD-10: C44 – Cutaneous squamous cell carcinoma.

ICD-11: 2C31 – Keratoacanthoma.

WHO Classification of Skin Tumours (4th Edition, Volume 11, 2018) recognizes keratoacanthoma within the spectrum of keratinocytic tumors, including well-differentiated squamous cell carcinoma, keratoacanthoma type, and keratoacanthoma-like squamous cell carcinoma⁶.

ICD-O code: 8071/3.

Synonyms include sebaceous molluscum, horn molluscum, pseudocarcinomatous molluscum, and Gougerot's epithelioma-like verrucoma.

Management of KA is guided by lesion-specific and patient-related factors, including tumor size, anatomical location, growth dynamics, and histopathological

findings^{7,8}. Although spontaneous regression may occur, the unpredictability of disease course and the potential for aggressive behavior support active therapeutic intervention in many cases.

Surgical excision remains the treatment of choice, while intralesional and other conservative modalities may be considered in selected patients^{7,8,19}.

Current management strategies emphasize a multidisciplinary approach integrating clinical, dermoscopic, and histopathological assessment to ensure diagnostic accuracy and appropriate therapeutic selection^{1,7,18}. A central clinical challenge lies in distinguishing lesions with potential for spontaneous regression from those that may represent or evolve into cSCC^{1, 13, 21}.

This narrative review provides an updated synthesis of the current understanding of keratoacanthoma, with emphasis on its clinical presentation, diagnostic challenges, dermoscopic and histopathological features, and contemporary treatment strategies. In addition, we present clinical observations derived from routine dermatological practice, with particular emphasis on dermoscopic patterns that may aid diagnostic evaluation.

Clinical Manifestations and Differential Diagnosis

Keratoacanthoma (KA) is characterized by a relatively rapid clinical evolution that distinguishes it from many other cutaneous epithelial tumors. The lesion usually develops within several weeks and presents as a solitary, well-demarcated, dome-shaped or hemispherical nodule with a central keratin-filled crater. The surrounding skin may demonstrate variable erythema, inflammation, or induration.

The classical clinical appearance has been described as a “volcano-like” structure, reflecting the combination of peripheral epithelial proliferation and central keratin accumulation^{2,3,11,12}.

Figures 1–4 demonstrate the typical clinical presentation of keratoacanthoma in different patients, showing dome-shaped crateriform nodules with central hyperkeratotic plugs and well-defined borders. These characteristic clinical features are highly suggestive of KA; however, similar morphological findings may also be observed in well-differentiated cutaneous squamous cell carcinoma (cSCC), which creates a significant diagnostic challenge and requires further evaluation^{1,2,9,10}.



Figure 1,2



Figure 3,4

Figures 1–4. Classical clinical manifestations of keratoacanthoma in different patients, characterized by dome-shaped crateriform nodules with central hyperkeratotic plugs and well-defined margins.

The early stage of KA is usually represented by a rapidly enlarging erythematous papule or nodule that gradually develops central hyperkeratosis. During the proliferative phase, lesions may increase in size over a short period of time and may reach several millimeters or more in diameter. KA most commonly occurs on chronically sun-exposed areas, including the face, ears, dorsal hands, and forearms, although lesions may develop at other anatomical sites ^{2,3,5}.

Clinically, KA may demonstrate different morphological variants. In addition to the classical solitary form, giant, multiple, eruptive, and atypical variants have been described. These forms may lack the typical crateriform appearance and can present a greater diagnostic challenge, particularly when the clinical picture resembles invasive cSCC or other keratinizing tumors ^{3,4,14,16,17}.

Figure 5 demonstrates a giant keratoacanthoma, representing a clinically distinct variant characterized by marked enlargement, prominent keratinization, and a large crateriform structure. Giant KA may show more extensive local involvement and therefore requires careful assessment to exclude malignant transformation and other aggressive keratinizing tumors ^{4,14}.



Figure 5. Giant keratoacanthoma showing a large crateriform lesion with a central keratin plug.

Figure 6 shows keratoacanthoma presenting as a cutaneous horn. This variant is characterized by excessive accumulation of compact keratin material forming a horn-like projection and may clinically overlap with other hyperkeratotic lesions, including squamous cell carcinoma ^{2,5,6}.



Figure 6. Clinical presentation of keratoacanthoma in the form of a cutaneous horn.

Figure 7 illustrates an atypical clinical localization of KA on the anterior abdominal wall. Although KA predominantly develops on sun-exposed areas, lesions may occasionally occur on less typical anatomical sites, which may complicate clinical recognition and differential diagnosis [3,5].



Figure 7. Clinical presentation of keratoacanthoma on the anterior abdominal wall.

The main differential diagnosis of KA includes cSCC, particularly well-differentiated variants, because both tumors may present as rapidly growing keratinizing nodules with central crusting or keratin accumulation. Clinical criteria alone are often insufficient to reliably distinguish between these entities, and histopathological examination remains essential for establishing the final diagnosis ^{1,2,9,10,21}.

Suspicious clinical features such as progressive enlargement, ulceration, bleeding, pain, or persistent growth may indicate the need for biopsy and further pathological assessment.

Other lesions that may mimic KA include irritated seborrheic keratosis, verruca vulgaris, giant molluscum contagiosum, prurigo nodularis, and some adnexal tumors. Inflammatory and infectious lesions may also occasionally simulate KA, particularly when ulceration, crusting, or marked hyperkeratosis are present^{2,5,6}.

Therefore, clinical examination remains the first and essential step in the diagnostic pathway. Recognition of both typical and atypical clinical patterns allows appropriate selection of biopsy technique, interpretation of dermoscopic findings, and planning of the most suitable treatment strategy.

Because of the close clinical and histopathological relationship between KA and cSCC, a combined clinical, dermoscopic, and histological approach is required for accurate diagnosis and optimal patient management^{1,2,7,18}.

Dermoscopic Features

Dermoscopy has become an important non-invasive tool in the evaluation of keratoacanthoma (KA), providing morphological details that may not be fully appreciated during routine clinical examination. Because of the substantial clinical overlap between KA and cutaneous squamous cell carcinoma (cSCC), dermoscopic assessment serves as a valuable adjunctive method in the diagnostic process^{18,20}.

The dermoscopic appearance of KA reflects its characteristic crateriform architecture. One of the most common findings is a central keratin-filled area, appearing as a homogeneous yellow-white amorphous structure corresponding to the clinically visible hyperkeratotic plug. This central keratinization is frequently surrounded by vascular structures located predominantly at the periphery of the lesion^{18,20}.

Several dermoscopic features have been repeatedly described in KA, including white circles surrounding follicular openings, white structureless areas, central keratin masses, keratin scales, blood spots, and polymorphous vascular patterns. Among the vascular structures, hairpin vessels, linear irregular vessels, and occasionally branching vessels are most frequently observed. These findings reflect active epithelial proliferation and tumor-associated vascular remodeling and contribute to the characteristic dermoscopic appearance of KA^{18,20}.

The combination of central keratin accumulation, white circles, white structureless zones, and peripheral hairpin or linear irregular vessels creates a pattern that is highly suggestive of KA. Nevertheless, significant overlap exists with well-differentiated cSCC, and dermoscopic findings should always be interpreted in conjunction with clinical and histopathological data^{18,20}. Figure 8 presents a schematic summary of the principal dermoscopic features of KA.

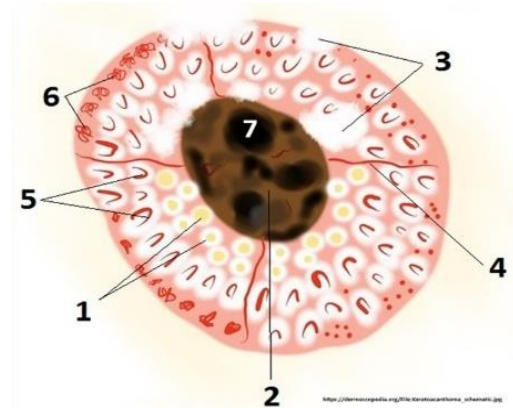


Figure 8. Schematic representation of dermoscopic features of keratoacanthoma.

Figure 9 demonstrates the typical dermoscopic appearance of keratoacanthoma observed in our clinical practice, including central keratinization and peripheral vascular structures.

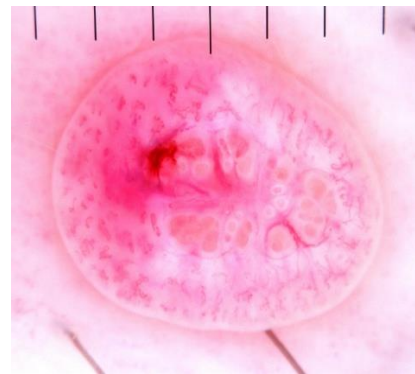


Figure 9. Dermoscopic appearance of keratoacanthoma showing central keratinization and peripheral vascular structures.

Figures 10–1# illustrate dermoscopic findings obtained from patients evaluated and documented as part of the authors' own clinical experience. These original clinical images demonstrate the spectrum of dermoscopic manifestations observed in routine clinical practice, including variations in keratinization, vascular morphology, white circles, structureless white areas, and blood spots.

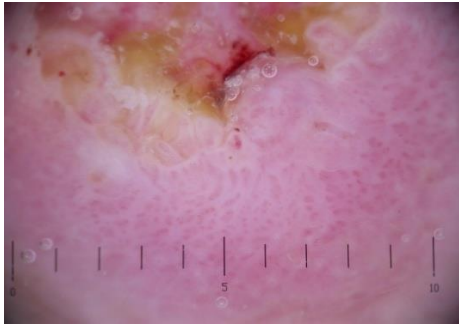


Figure 10.

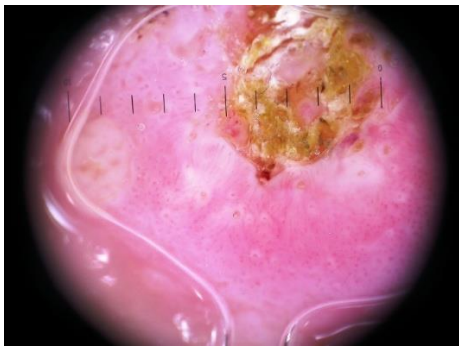


Figure 11.



Figure 12.



Figure 13.

Figures 10–13. Dermoscopic manifestations of keratoacanthoma in different clinical cases from the authors' clinical archive.

Correlation between clinical morphology and dermoscopic findings is particularly important in

everyday practice. Dermoscopy allows better visualization of lesion architecture, facilitates selection of the most representative biopsy site, and improves diagnostic confidence when evaluating crateriform tumors^{18,20}.

Compared with KA, cSCC often demonstrates greater structural asymmetry, more chaotic vascular patterns, irregular ulceration, and heterogeneous keratin distribution. However, no single dermoscopic criterion is sufficiently specific to establish a definitive diagnosis. Consequently, histopathological examination remains mandatory whenever diagnostic uncertainty persists^{1,18,20}.

In our experience, dermoscopy played a central role in the assessment of suspected KA. The presence of crateriform architecture, central keratinization, white circles, and characteristic vascular patterns frequently guided biopsy planning and contributed to subsequent therapeutic decision-making.

The integration of clinical examination, dermoscopy, and histopathological evaluation provided a reliable diagnostic approach in our clinical practice.

Histopathology and Diagnostic Criteria

Histopathological examination remains the reference method for confirming the diagnosis of keratoacanthoma (KA).

Despite the availability of clinical and dermoscopic criteria, differentiation between KA and well-differentiated cutaneous squamous cell carcinoma (cSCC) often remains difficult because these lesions share many overlapping morphological features [1,2,5].

Microscopically, KA is characterized by a relatively symmetrical crateriform lesion with a central keratin-filled crater and proliferating squamous epithelium extending into the dermis. One of the most characteristic architectural features is epidermal lipping, also referred to as buttressing, in which the epidermis extends over the edges of the crater. The epithelial lobules are usually broad and well circumscribed, showing a pushing rather than infiltrative growth pattern. Keratinocytes commonly possess abundant eosinophilic “glassy” cytoplasm, reflecting a high degree of squamous differentiation. Together with the overall symmetry of the lesion, these features are considered helpful diagnostic clues favoring KA over invasive cSCC^{1,5,21}.

The histological appearance varies according to the stage of tumor development. In the proliferative phase,

marked acanthosis and epithelial hyperplasia are observed, accompanied by active keratinocyte proliferation and progressive formation of the characteristic crateriform architecture. As the lesion matures, keratinization becomes more pronounced, and the overall structure acquires the typical volcano-like configuration recognized clinically^{1,3}.

Cytological atypia in KA is usually mild or moderate. Mitotic figures may be present, particularly in the peripheral proliferative zones, and a mixed inflammatory infiltrate is frequently observed within the adjacent dermis. These findings should not be interpreted in isolation, as individual cytological features may overlap with those seen in cSCC. Instead, assessment of the overall architectural pattern remains essential for accurate diagnosis^{1,5}.

Distinguishing KA from well-differentiated cSCC represents the principal diagnostic challenge. Features that favor cSCC include irregular infiltrative growth, destruction of surrounding dermal structures, marked nuclear pleomorphism, atypical mitotic figures, perineural invasion, and loss of the characteristic symmetrical crateriform architecture. Nevertheless, some lesions display overlapping histological characteristics, and in certain cases a definitive distinction may be difficult even after thorough pathological examination^{1,5,21}.

Adequate tissue sampling is critical for reliable diagnosis. Superficial shave biopsies or limited specimens may fail to capture the overall architecture of the lesion, resulting in diagnostic uncertainty. For this reason, deep and representative biopsy samples that include both the central crater and peripheral margins are recommended whenever KA is suspected^{2,5}.

Immunohistochemical markers such as Ki-67, p53, p16, Bcl-2, and COX-2 have been investigated as potential adjunctive tools in the differential diagnosis between KA and cSCC. Although differences in expression patterns have been reported, considerable overlap exists, and no marker has demonstrated sufficient diagnostic accuracy to replace conventional histopathological assessment. Consequently, immunohistochemistry should be regarded as a supportive rather than definitive diagnostic method^{1,8}.

In clinical practice, the diagnosis of keratoacanthoma is best established through clinicopathological correlation. Integration of clinical presentation, dermoscopic findings, and histopathological features provides the most reliable approach for distinguishing KA from cSCC and for selecting the most appropriate therapeutic strategy^{1,2,5}.

Therefore, the diagnosis of KA should be considered a clinicopathological process rather than a purely microscopic diagnosis. Integration of clinical morphology, dermoscopy, and histology allows a more accurate assessment of biological behavior and supports appropriate treatment selection^{1,2,5}.

Individualized treatment strategy

The management of keratoacanthoma (KA) continues to generate discussion among dermatologists because the biological behavior of these tumors is not always predictable. Although spontaneous regression has been documented in some cases, it is impossible to determine with certainty which lesions will regress and which may continue to grow or exhibit features resembling cutaneous squamous cell carcinoma (cSCC). As a result, treatment decisions should not rely solely on the possibility of spontaneous involution but rather on a comprehensive assessment of clinical, dermoscopic, and histopathological findings^{1,3,7}.

The choice of treatment depends on multiple factors, including lesion size, anatomical location, growth rate, clinical appearance, patient age, associated comorbidities, cosmetic considerations, and the degree of diagnostic certainty. In routine clinical practice, management should be individualized, as no single therapeutic strategy is appropriate for all patients^{3,5,8}.

Surgical Treatment

Surgical excision remains the most widely accepted treatment option and is considered the preferred approach in many clinical settings. Its main advantage is that it provides both complete lesion removal and the opportunity for thorough histopathological evaluation. This is particularly important in cases where differentiation from well-differentiated cSCC remains uncertain despite clinical and dermoscopic examination^{1,7}.

Conventional excision is effective for most lesions and allows assessment of tumor margins as well as the depth and architectural characteristics of the lesion. Surgical treatment is generally preferred for rapidly enlarging tumors, recurrent lesions, atypical presentations, large keratoacanthomas, and tumors arising in locations where invasive carcinoma cannot be confidently excluded^{1,5,7}. In anatomically sensitive areas such as the nose, eyelids, lips, ears, and digits, Mohs micrographic surgery may offer additional advantages. By allowing precise margin control while preserving healthy surrounding tissue, Mohs surgery can provide optimal functional and cosmetic outcomes in selected patients⁷.

Intralesional Therapies

During recent years, increasing attention has been directed toward intralesional treatment modalities, particularly in patients for whom surgery may not be the most appropriate option. Intralesional methotrexate has demonstrated favorable results in numerous reports and has become one of the most frequently used conservative treatment approaches for selected cases of KA. Significant reduction in lesion size may occur after one or several injections, especially in elderly patients, individuals with multiple lesions, or patients with medical conditions that increase surgical risk ^{7,8}.

Intralesional 5-fluorouracil (5-FU) has also been used successfully in the treatment of KA. By interfering with DNA synthesis in rapidly proliferating keratinocytes, 5-FU may induce gradual tumor regression while preserving surrounding tissue. This approach may be particularly useful when lesions are located in cosmetically sensitive areas or when surgical intervention would result in significant tissue loss ^{7,8,19}.

Although the available evidence is largely based on case reports and small clinical series, both methotrexate and 5-FU have emerged as valuable therapeutic alternatives in carefully selected patients and represent important components of contemporary KA management ^{7,8}.

Cryotherapy and Laser-Based Approaches

Cryotherapy remains a useful option for selected small and well-circumscribed lesions. Controlled tissue destruction by freezing may achieve satisfactory clinical outcomes while avoiding more invasive procedures. Nevertheless, because clinical and dermoscopic findings alone may not always distinguish KA from cSCC, histopathological confirmation should ideally be obtained before destructive treatment is undertaken ^{5,7}.

Laser-based methods, particularly CO₂ laser ablation, have also been reported as effective in selected cases. Laser treatment may be considered for superficial lesions and for tumors located in areas where cosmetic outcome is an important concern. However, because laser ablation destroys tissue and may limit subsequent histopathological evaluation, careful patient selection remains essential ^{7,8}.

Systemic Treatment

Systemic therapy is rarely required in patients with solitary keratoacanthoma but may play an important role in individuals with multiple eruptive lesions or

inherited forms of the disease. Oral retinoids, particularly acitretin, have shown beneficial effects in reducing lesion burden and decreasing the development of new tumors. Such treatment may be especially useful in patients with Ferguson–Smith syndrome, generalized eruptive keratoacanthomas, and other rare forms characterized by multiple recurrent lesions ^{15–17}.

Factors Influencing Treatment Selection

Selection of the most appropriate therapeutic approach begins with an accurate diagnosis and careful evaluation of the likelihood of cSCC. Clinical features such as rapid enlargement, ulceration, recurrence, tissue destruction, persistent growth, or histopathological findings suggestive of malignancy generally favor definitive surgical management ^{1,5,21}.

On the other hand, conservative treatment approaches may be appropriate for selected patients with small lesions, multiple tumors, advanced age, significant comorbidities, or lesions located in anatomically and cosmetically sensitive regions. In these situations, treatment should balance oncological safety with preservation of function and appearance ^{3,7,8}.

The clinical material presented in this review reflects the authors' clinical experience in the evaluation and management of patients with keratoacanthoma.

As dermatologists, our primary focus has been the accurate clinical and dermoscopic diagnosis of keratoacanthoma and the development of an individualized treatment strategy based on the specific characteristics of each lesion. Dermoscopy has become an integral part of our routine evaluation and frequently provides valuable information beyond that obtained by clinical examination alone. Particular attention is paid to lesion symmetry, crateriform architecture, central keratinization, white circles, white structureless areas, blood spots, and characteristic vascular patterns. Correlation of these findings with the clinical presentation often improves diagnostic confidence and facilitates differentiation between KA and other keratinizing tumors, especially well-differentiated cSCC ^{18,20}.

The dermoscopic images presented in this study were obtained from patients evaluated in routine clinical practice and documented as part of the authors' clinical experience. In our experience, dermoscopy is especially valuable in atypical cases and frequently assists in selecting the most representative site for biopsy and histopathological evaluation ^{18,20}.

Unlike surgical disciplines, our clinical approach has

primarily emphasized conservative and tissue-preserving management whenever such treatment could be applied safely. Intralesional methotrexate, intralesional 5-fluorouracil, cryotherapy, and other non-surgical modalities were frequently considered in patients with favorable clinicodermoscopic characteristics, particularly in elderly individuals, patients with significant comorbidities, and those with lesions located in cosmetically sensitive areas ^{7,8,19}.

Surgical treatment was reserved mainly for lesions demonstrating rapid progression, recurrence, destructive growth, diagnostic uncertainty, or histopathological features raising suspicion for cSCC. In these circumstances, complete excision remained necessary both for therapeutic purposes and for definitive pathological assessment ^{1,5,7,21}.

Our experience suggests that careful clinicodermoscopic evaluation allows more accurate treatment stratification and may reduce the need for unnecessary surgical procedures in selected patients. The combination of clinical examination, dermoscopy, and histopathological verification remains the cornerstone of effective management and supports a personalized approach to patients with keratoacanthoma ^{1,2,18,20}.

DISCUSSION

Keratoacanthoma (KA) remains one of the most challenging keratinizing epithelial tumors encountered in dermatological practice because of its close clinical, dermoscopic, and histopathological relationship with cutaneous squamous cell carcinoma (cSCC). The findings from the current literature together with our clinical observations indicate that KA cannot always be regarded as a predictable self-limiting lesion. Although spontaneous regression is a well-recognized feature of KA, the clinical course may vary considerably, and some lesions may persist, continue to enlarge, or demonstrate characteristics overlapping with invasive cSCC ^{1,3,5}.

The major diagnostic challenge in KA is the absence of a single clinical, dermoscopic, or histopathological criterion that can reliably distinguish it from well-differentiated cSCC in every patient. Both conditions may present with rapidly growing crateriform nodules, central keratinization, and inflammatory changes. Based on our review of the literature and our own clinical experience, the most reliable diagnostic approach is the integration of clinical morphology, dermoscopy, and histopathological examination rather than reliance on an isolated diagnostic feature ^{1,2,18}.

Dermoscopy has become an important part of the diagnostic assessment of KA because it provides additional information regarding tumor architecture and surface characteristics that may not be clearly visible on routine examination. In our clinical observations, the most characteristic dermoscopic findings included a central keratin-filled area, white structureless zones, white circles, blood spots, and peripheral vascular patterns, including hairpin and irregular vessels. These findings reflected the typical crateriform organization of KA and helped identify lesions requiring biopsy and further evaluation ^{18,20}.

The dermoscopic images included in this review were obtained from patients evaluated in routine dermatological practice and represent the range of dermoscopic patterns observed in keratoacanthoma. Our clinical observations are in agreement with previously described dermoscopic features of KA and highlight the practical importance of dermoscopy in daily diagnostic decision-making. In our experience, dermoscopic assessment contributed not only to improved diagnostic confidence but also to the selection of an appropriate biopsy site and the planning of individualized management strategies ^{18,20}.

Histopathological examination remains essential because dermoscopic findings of KA may overlap with those observed in cSCC. The symmetrical crateriform architecture, central keratin-filled cavity, epidermal lipping, buttress-like epithelial proliferation, pushing borders, and well-differentiated keratinocytes with glassy eosinophilic cytoplasm represent characteristic features supporting the diagnosis of KA. In contrast, irregular infiltrative growth, destructive invasion, marked cytological atypia, abnormal mitotic activity, and perineural involvement should raise concern for cSCC. Our experience confirms that adequate biopsy sampling, including both the central and peripheral components of the lesion, is necessary for correct histopathological interpretation ^{1,5,21}.

The therapeutic approach to KA is closely related to diagnostic certainty and assessment of the biological risk of each lesion. Although surgical excision remains the preferred treatment in many cases, particularly when cSCC cannot be excluded or when aggressive clinical features are present, treatment decisions should not be based only on tumor removal. In our practice as dermatologists, the choice of therapy is guided by the combination of clinical morphology, dermoscopic findings, histopathological results, lesion localization, and patient-related factors ^{1,7}.

In selected patients, especially elderly individuals, patients with multiple lesions, or cases involving

cosmetically and functionally sensitive areas, non-surgical approaches may provide important advantages. Intralesional therapies such as methotrexate and 5-fluorouracil, together with other conservative methods, may achieve satisfactory clinical responses while reducing unnecessary tissue loss. However, these approaches should only be considered after appropriate diagnostic evaluation and should not replace histopathological confirmation in uncertain cases ^{7,8,19}.

Our clinical observations suggest that KA should not be managed solely on the assumption that spontaneous regression will occur. A conservative strategy may be appropriate only after careful assessment of clinical behavior and dermoscopic characteristics. Conversely, lesions demonstrating rapid enlargement, recurrence, ulceration, destructive changes, or suspicious histological findings require active treatment to avoid delayed management of tumors with malignant potential ^{1,5,21}.

The combination of dermoscopy and histopathology in our practice improved diagnostic accuracy and supported individualized treatment selection. This integrated approach allows clinicians to avoid unnecessary aggressive procedures in selected patients while maintaining appropriate oncological safety when cSCC remains a concern ^{1,2,18}.

Future research should focus on identifying reliable molecular, genetic, and clinical predictors that may better define the biological behavior of KA and clarify its relationship with cSCC. Further refinement of dermoscopic criteria, development of advanced imaging techniques, and identification of molecular markers may contribute to improved risk stratification and more personalized therapeutic decisions ^{1,8}.

Overall, our findings support the concept that KA requires careful clinical judgment and should not be considered either a uniformly benign or uniformly malignant lesion. A combined clinicodermoscopic and histopathological approach, together with individualized treatment planning, represents the most practical strategy for achieving accurate diagnosis and optimal patient management ^{1,2,18,20}.

Limitations

This narrative review has several limitations that should be considered when interpreting the presented findings. The available literature on keratoacanthoma (KA) remains heterogeneous regarding diagnostic criteria, classification systems, and therapeutic approaches. The lack of universally accepted criteria that clearly separate KA from well-differentiated cutaneous

squamous cell carcinoma (cSCC) continues to be a major challenge and limits direct comparison between published studies ^{1,5}.

Another limitation is the variability of available clinical evidence. Many studies evaluating KA are based on retrospective analyses, case reports, or relatively small patient cohorts. The unpredictable clinical course of KA, including spontaneous regression in some patients and persistent or progressive behavior in others, makes it difficult to establish uniform treatment recommendations applicable to all clinical situations ^{3,7}.

The diagnostic overlap between KA and cSCC represents an additional limitation. Although clinical examination, dermoscopy, and histopathological assessment have significantly improved diagnostic accuracy, some lesions continue to demonstrate overlapping characteristics. Dermoscopic findings such as central keratinization, white structureless areas, white circles, vascular patterns, and crateriform architecture may support the diagnosis of KA but cannot completely exclude cSCC without histological confirmation ^{1,18,20}.

A further limitation concerns the interpretation of treatment outcomes. Since therapeutic decisions depend on lesion characteristics, anatomical localization, patient age, comorbidities, and clinician experience, comparison between different treatment modalities remains difficult. Prospective studies with standardized diagnostic criteria and long-term follow-up are required to better define the indications and effectiveness of surgical and non-surgical approaches ^{7,8}.

Regarding our clinical experience, the presented observations reflect routine dermatological practice and the diagnostic experience of the authors in routine dermatological practice.

As with any clinical experience from a single medical center, the findings may be influenced by patient selection, referral patterns, and characteristics of the examined population. Nevertheless, the integration of clinical evaluation, dermoscopy, and histopathology provided valuable practical information for individualized KA management. Further multicenter studies with larger patient groups are needed to validate these observations and establish more precise diagnostic and therapeutic algorithms.

Future Perspectives and Conclusion

Future research should focus on improving the understanding of the biological relationship between keratoacanthoma and cutaneous squamous cell

carcinoma. Identification of reliable molecular and genetic markers may help predict lesion behavior and allow earlier differentiation between lesions with a self-limited course and those with malignant potential^{1,8}.

Further development of standardized dermoscopic criteria may improve the diagnostic pathway of KA. Our clinical experience suggests that dermoscopy serves as an important link between clinical examination and histopathology by allowing better evaluation of lesion architecture, keratinization patterns, and vascular structures. Future studies combining dermoscopic imaging with digital analysis may further improve diagnostic precision and reduce unnecessary invasive procedures.

From a therapeutic perspective, future investigations should aim to define clearer indications for different treatment strategies. While surgical excision remains an important option, particularly when cSCC cannot be excluded, minimally invasive approaches such as intralesional methotrexate, intralesional 5-fluorouracil, cryotherapy, and other tissue-preserving methods may become increasingly valuable in carefully selected patients, especially those with multiple lesions, increased surgical risk, or tumors located in cosmetically sensitive areas^{7,8,19}.

In conclusion, keratoacanthoma remains a challenging keratinizing epithelial tumor because of its rapid growth, variable biological behavior, and close relationship with cSCC. The findings from the literature together with our clinical and dermoscopic observations support the need for a comprehensive diagnostic strategy combining clinical examination, dermoscopy, and histopathological confirmation.

Our experience emphasizes that KA management should not follow a uniform approach but should be individualized according to lesion morphology, dermoscopic characteristics, histological findings, anatomical location, and patient-related factors. Careful clinicodermoscopic assessment combined with appropriate histological evaluation allows more reliable diagnosis and rational treatment selection while maintaining a balance between oncological safety and preservation of cosmetic and functional outcomes^{1,2,18,20}.

DECLARATIONS

Competing Interests

The authors declare no conflict of interest.

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Ethical Approval

Informed consent was obtained from all patients. Retrospective clinical case documentation was reviewed and approved in accordance with ethical standards.

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ORIGINAL ARTICLE

COMPARISON OF PRF AND I-PRF IN WOUND HEALING FOLLOWING SURGICAL EXTRACTIONS OF MANDIBULAR THIRD MOLARS

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Abstract

Background: Surgical extraction of impacted mandibular third molars is frequently associated with postoperative complications, including pain, delayed soft-tissue healing, periodontal pocket formation, and swelling. Autologous platelet concentrates, particularly platelet-rich fibrin (PRF) and injectable platelet-rich fibrin (I-PRF), have gained increasing attention due to their potential regenerative properties and ability to enhance tissue repair and postoperative healing.

Aim: To compare the effectiveness of PRF and I-PRF in enhancing wound healing following surgical extraction of impacted mandibular third molars.

Materials & Methods: A randomized, double-blind, split-mouth clinical study was conducted among 21 patients requiring bilateral surgical extraction of impacted mandibular third molars, resulting in a total of 42 extraction sockets. Each patient received both interventions: one extraction site was treated with PRF, while the contralateral site was treated with I-PRF according to a computer-generated randomization sequence. Postoperative pain, soft-tissue healing, swelling, periodontal pocket formation, and maximum interincisal mouth opening were assessed at predetermined follow-up intervals. Statistical analysis was performed using SPSS version 26. Intergroup comparisons were performed using the paired t-test and Wilcoxon Signed-Rank test, according to the distribution of the data.

Results: The I-PRF-treated sites demonstrated significantly improved early postoperative healing outcomes compared with PRF-treated sites. Postoperative pain scores were significantly lower in the I-PRF group on postoperative day 1 ($p = 0.001$) and day 3 ($p = 0.002$), whereas no significant difference was observed on day 7 ($p = 0.72$). Soft-tissue healing scores were significantly higher in the I-PRF group on day 3 ($p = 0.003$) and day 7 ($p = 0.001$). Postoperative swelling was significantly reduced in the I-PRF group compared with PRF-treated sites on days 3, 7, and 14 ($p < 0.05$). Periodontal pocket depth was significantly lower in the I-PRF group on day 7 ($p = 0.001$) and day 14 ($p = 0.002$). No significant differences were observed between groups regarding maximum interincisal mouth opening during the follow-up period.

Conclusion: Within the limitations of this study, both PRF and I-PRF demonstrated beneficial effects on postoperative healing following surgical extraction of impacted mandibular third molars. However, I-PRF provided superior early soft-tissue healing, reduced postoperative pain and swelling, and decreased periodontal pocket formation compared with conventional PRF. The findings suggest that I-PRF may represent a valuable adjunctive regenerative approach for improving early postoperative outcomes after third molar surgery.

Keywords: Platelet-rich fibrin; Injectable platelet-rich fibrin; Impacted mandibular third molar; Wound healing; Surgical extraction; Regenerative dentistry.

INTRODUCTION

Lower third molar extraction, also known as wisdom tooth extraction, is a routine minor surgical procedure performed in oral and maxillofacial surgery. Although it is generally considered a safe procedure, several postoperative complications may occur, including periodontal pocket formation, delayed wound healing, postoperative pain, swelling, and alveolar osteitis (AO). These complications may negatively affect the patient's postoperative experience by causing discomfort, prolonging recovery time, and, in some cases, increasing the risk of secondary infections. To overcome these limitations and enhance tissue regeneration, regenerative medicine has focused on platelet-rich fibrin (PRF) and its injectable form, injectable platelet-rich fibrin (I-PRF).

PRF is an autologous platelet concentrate prepared from the patient's own blood. Unlike earlier platelet concentrate techniques, PRF is produced without the use of anticoagulants, allowing the formation of a natural fibrin matrix. This fibrin matrix acts as a biological scaffold enriched with platelets, leukocytes, and various growth factors. When placed into the extraction socket, PRF promotes angiogenesis, enhances new blood vessel formation, reduces inflammation, and supports the healing process of soft tissue and bone.

Injectable Platelet-Rich Fibrin (I-PRF): Biological Properties and Clinical Applications

While conventional PRF is obtained as a solid fibrin membrane, injectable platelet-rich fibrin (I-PRF) represents a liquid formulation that provides greater flexibility in clinical applications. Due to its liquid state, I-PRF remains injectable for a short period before polymerization and clot formation, allowing clinicians to:

1. Inject it directly into the surgical site.
2. Combine it with bone graft materials to create a biologically active regenerative mixture.
3. Deliver a concentrated amount of cytokines and growth factors directly to the wound area.

I-PRF may enhance clot stabilization and improve the distribution of regenerative components within the extraction socket. For patients, this may result in reduced postoperative pain, decreased swelling, improved wound healing, and a lower risk of complications such as dry socket.

Aim

The present study was designed to compare the effectiveness of injectable platelet-rich fibrin (I-PRF) and conventional platelet-rich fibrin (PRF) in improving postoperative outcomes following surgical extraction of impacted mandibular third molars, including pain, swelling, soft-tissue healing, and periodontal pocket formation.

Objectives

1. To assess postoperative pain in the PRF and I-PRF groups.
2. To evaluate soft-tissue healing in the PRF and I-PRF groups.
3. To assess postoperative swelling in the PRF and I-PRF groups.
4. To evaluate periodontal pocket formation in the PRF and I-PRF groups.
5. To compare postoperative pain, soft-tissue healing, swelling, and mouth opening between the PRF and I-PRF groups.

MATERIALS AND METHODS

Study Design

A randomized, double-blind, split-mouth clinical study was conducted in the Department of Oral and Maxillofacial Surgery, SIBAR Institute of Dental Sciences, between June 2025 and August 2025. A total of 21 patients aged 18–45 years requiring bilateral surgical extraction of impacted mandibular third molars (Pell and Gregory Class I, Position A) were enrolled in the study.

As each patient contributed two extraction sockets, a total of 42 extraction sites were included. In the split-mouth study design, one extraction socket received platelet-rich fibrin (PRF), while the contralateral extraction socket received injectable platelet-rich fibrin (I-PRF). Both mandibular third molars were surgically removed during the same appointment, allowing each patient to serve as their own control and minimizing inter-individual variability.

All participants were informed about the nature, objectives, and procedures of the study, and written informed consent was obtained before enrolment. Ethical approval was obtained from the Institutional Ethics Committee (Reference No. 04/IEC-SIBAR/CIR/25).

Randomization and Blinding

A computer-generated randomization sequence was used to allocate PRF and I-PRF treatments to the extraction sites. One side was randomly assigned to receive PRF, while the contralateral side received I-PRF. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes, which were opened immediately before placement of the platelet concentrate. The study followed a double-blind design. Patients were unaware of the treatment allocated to each extraction site, and the investigator responsible for postoperative assessment was blinded to the intervention. The surgeon performing the procedure was aware of the material being placed due to differences in preparation and handling techniques; however, the surgeon was not involved in postoperative outcome assessment.

Follow-up

Patients were evaluated postoperatively on days 1, 3, 7, and 14. Clinical parameters, including postoperative pain, soft-tissue healing, swelling, and periodontal pocket formation, were assessed during the follow-up period. All enrolled patients completed the scheduled follow-up visits.

Eligibility Criteria

Inclusion Criteria

- Individuals aged 18–45 years.
- Patients categorized as ASA Physical Status I or II.
- Presence of bilateral impacted mandibular third molars requiring surgical extraction (Pell and Gregory Class I, Position A).
- Patients willing to participate and comply with the follow-up evaluation schedule.

Exclusion Criteria

- Systemic diseases or medical conditions known to impair healing or contraindicate oral surgical procedures, including uncontrolled diabetes mellitus and bleeding disorders.
- Pregnant or breastfeeding women.
- Patients receiving medications that could influence coagulation or tissue repair.
- Presence of acute infection at the intended surgical site.

Surgical Procedure

All procedures were performed under local anesthesia following a standardized surgical protocol. A

mucoperiosteal flap was reflected to expose the impacted tooth, followed by bone removal and tooth sectioning whenever required. After extraction, the socket was thoroughly irrigated with sterile saline solution to remove debris and bone particles. For the PRF group, 10 mL of venous blood was collected without the use of an anticoagulant and centrifuged at 3000 rpm for 10 minutes (Figure 1).



Figure 1. Centrifuged blood samples in test tubes showing the separation of platelet-rich fibrin (PRF)

The resulting fibrin clot was separated and compressed to form a PRF membrane, which was subsequently placed into the extraction socket (Figure 2).



Figure 2. Extracted PRF matrix from the test tubes

In the PRF group, PRF matrix is placed in the socket of extracted tooth (Figure 3,4).



Figure 3. Placement of PRF in the extracted socket with the help of tissue holding forceps



Figure 4. Placed PRF in the extracted socket

For the I-PRF group, 10 mL of venous blood was collected and centrifuged at 700 rpm for 3 minutes. The upper orange-coloured liquid layer was aspirated and used as injectable platelet-rich fibrin (I-PRF) (Figure 5,6).



Figure 5. Centrifuged blood samples in test tubes showing the separation of Injectable platelet-rich fibrin (I-PRF)



Figure 6. Extracted I-PRF in the syringe from the test tubes

The prepared I-PRF was immediately injected into the contralateral extraction socket following tooth removal and socket irrigation (Figure 7).



Figure 7. Placement of I-PRF in the extracted socket.

Subsequently, all surgical sites were closed using 3-0 silk sutures to facilitate wound stabilization and postoperative healing (Figure 8).



Figure 8. Closure of the extraction socket

Measurements were recorded to evaluate the degree of postoperative edema and to compare changes in swelling between the PRF-treated and I-PRF-treated extraction sites. Swelling assessment was performed during the early healing period, including postoperative days 3, 7, and 14.

Outcome Assessment

Pain Assessment

Postoperative pain intensity was recorded using a 10-point Visual Analogue Scale (VAS), where higher scores indicated greater pain severity. Assessments were performed on postoperative days 1, 3, and 7.

Swelling Assessment

Facial swelling was evaluated through clinical measurements obtained at baseline and during follow-up visits.

Soft-Tissue Healing Assessment

Healing of the surgical site was assessed using a standardised wound-healing index (Laundry) that considered tissue appearance, epithelialization, and overall wound closure. Evaluations were carried out on postoperative days 3 and 7.

Periodontal Pocket Depth Assessment

Periodontal pocket depth adjacent to the extraction site was measured in millimetres using a graduated periodontal probe. Measurements were recorded during follow-up to assess periodontal healing.

Statistical Analysis

Data were analysed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean $\pm$ standard deviation (SD). The normality of continuous variables was assessed using the Shapiro–Wilk test. Variables demonstrating a normal distribution were analysed using the paired t-test, whereas variables not following a normal distribution were analyzed using the Wilcoxon Signed-Rank test. Pain scores, soft-tissue healing scores, and periodontal pocket depth measurements were compared between the PRF and I-PRF groups. A p-value of less than 0.05 was considered statistically significant

RESULTS

I-PRF significantly reduced pain compared to PRF ($p < 0.05$), showing improved early pain control. By day seven, there is no significant difference in the pain levels between the two groups.

Table 1. Postoperative Pain

Day	PRF	I-PRF	p-value
1	6.0 ± 1.2	4.0 ± 1.0	0.001*
3	4.0 ± 1.1	2.0 ± 0.9	0.002*
7	1.0 ± 0.5	1.0 ± 0.4	0.72

Table 2. Soft Tissue Healing

Day	PRF	I-PRF	p-value
3	2.0 ± 0.6	3.0 ± 0.7	0.003*
7	4.0 ± 0.5	5.0 ± 0.5	0.001*

At both Day 3 and Day 7, I-PRF showed significantly superior soft tissue healing scores compared to PRF ($p < 0.05$)

Table 3. Pocket Formation

Day	PRF (mm)	I- PRF (mm)	p-value
Day 7	2.2 ± 0.4	1.6 ± 0.3	0.001 *
Day 14	1.8 ± 0.3	1.2 ± 0.2	0.002 *

The I-PRF group had less pocket formation, with a statistically significant p -value > 0.05 .

Table 4. Postoperative swelling

Day	PRF (mm)	I- PRF (mm)	p-value
Day 3	12.4 ± 2.1 mm	8.6 ± 1.9 mm	0.003*
Day 7	7.8 ± 1.8 mm	4.9 ± 1.5 mm	0.001*
Day 14	3.5 ± 1.1 mm	2.1 ± 0.9 mm	0.012*

Postoperative swelling gradually decreased in both groups during the healing period. However, the I-PRF group consistently demonstrated lower swelling measurements than the PRF group at all follow up visits.

The differences were statistically significant on Days 3, 7, and 14 ($p < 0.05$), indicating improved control of postoperative swelling with I-PRF.

Table 5. Comparison of Maximum Interincisal Mouth Opening Between Groups

Day	PRF (mm)	I- PRF (mm)	p-value
Day 3	29.4 ± 4.1	30.2 ± 3.8	0.487
Day 7	36.8 ± 3.5	37.5 ± 3.2	0.534
Day 14	43.6 ± 2.9	44.1 ± 2.7	0.648

Mouth opening improved progressively in both groups during the postoperative period. No significant differences in trismus were observed between the PRF and I-PRF groups at Days 3, 7, or 14 ($p > 0.05$).

DISCUSSION

Trismus, postoperative pain, oedema, and delayed soft-tissue healing are well-recognized sequelae following surgical extraction of impacted mandibular third molars. These complications arise from the inflammatory cascade triggered by periosteal elevation, bone removal, and socket trauma¹. Autologous platelet concentrates have garnered increasing interest as adjuncts to socket management, as they deliver a supraphysiological concentration of growth factors — including platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF) — directly to the wound environment². The present split-mouth randomised study was designed to critically compare injectable platelet-rich fibrin (I-PRF) with conventional platelet-rich fibrin (PRF) in terms of postoperative pain, soft-tissue healing, swelling, and pocket formation following mandibular third molar surgery.

Platelet-Rich Fibrin (PRF) was introduced by Choukroun J et al. (2001) as a second-generation platelet concentrate that forms a dense fibrin matrix capable of progressively releasing growth factors at the surgical site³. Additionally, cellular migration and tissue regeneration are supported by the fibrin scaffold. Dohan DM et al. (2006) elaborated on the biological characteristics and regenerative potential of PRF, highlighting its capacity to promote bone regeneration and soft-tissue healing⁴.

Daugela P et al. (2018) observed that using PRF in extraction sockets reduced postoperative pain and swelling while increasing soft-tissue recovery following mandibular third molar surgery⁵. Similarly, Kumar N et al. (2015) found that patients treated with PRF after surgical extraction of impacted third molars had better postoperative recovery and faster healing⁶. The results of the current study are in accordance with the PRF group's satisfactory healing and reduced postoperative discomfort.

Emerging literature demonstrates that Injectable Platelet-Rich Fibrin (I-PRF) is generated by a low-speed centrifugation procedure. I-PRF was first proposed by Miron RJ et al. (2017). They reported that it has a greater concentration of leukocytes and platelets, which optimises its capacity for regeneration and induces angiogenesis and cellular migration⁷. I-PRF can be injected directly into tissues owing to its liquid state, which facilitates growth factor dispersion confined to the surgical site. The I-PRF group in the present study demonstrated significantly better early postoperative results, such as increased pain and swelling reduction and enhanced soft-tissue healing.

These findings are consistent with those of Tanya Nagrani et al. (2021), who investigated bone regeneration following tooth extraction and socket preservation and discovered that I-PRF enhanced bone healing and ridge preservation⁸. Similarly, PRF enhances bone and soft-tissue healing after mandibular third molar extraction, according to Manzoor Mohammad Dar et al. (2018)⁹. Additionally, Zwitter B et al. (2024) reported that the use of PRF facilitated postoperative recovery and minimised complications after third molar surgery¹⁰.

The superior performance of I-PRF observed in the present study can be attributed to several biological advantages over conventional PRF. The low-speed centrifugation protocol (700 rpm for 3 minutes) employed for I-PRF preparation yields a liquid concentrate that retains a significantly higher proportion of viable platelets, leukocytes, and mesenchymal stem cells compared to the high-speed protocol used for PRF. This is consistent with Miron RJ et al. (2017), who demonstrated that the reduced centrifugal force preserves platelet morphology and prevents premature degranulation, thereby maintaining the full growth factor payload for release at the wound site⁷. Furthermore, the liquid consistency of I-PRF allows it to permeate the three-dimensional architecture of the cancellous bone within the extraction socket, ensuring uniform growth factor distribution, an advantage that the solid PRF membrane, which acts primarily as a surface scaffold, cannot replicate. The resultant paracrine signaling by PDGF and TGF- β is likely responsible for the accelerated fibroblast proliferation, angiogenesis, and collagen synthesis observed in the I-PRF group, particularly on days 3 and 7 postoperatively.

While the statistical differences between I-PRF and PRF across pain ($p = 0.001$ – 0.002), soft-tissue healing ($p = 0.001$ – 0.003), and pocket formation ($p = 0.001$ – 0.002) were highly significant, it is important to critically appraise the clinical magnitude of these differences. The mean VAS pain score on day 1 was 6.0 ± 1.2 in the PRF group and 4.0 ± 1.0 in the I-PRF group a difference of 2 points. Although statistically significant, the minimal clinically important difference (MCID) for VAS pain is generally accepted to be 1.5–2.0 points; therefore, the observed difference falls at the lower boundary of clinical relevance. Similarly, by day 7, pain scores converged (1.0 vs 1.0, $p = 0.72$), indicating that the primary advantage of I-PRF is in early postoperative pain control rather than long-term pain reduction. Clinicians should, therefore, interpret I-PRF's superiority as an early-phase benefit with limited long-term differentiation from conventional PRF. The reduced pocket formation in the I-PRF group (1.6 mm vs 2.2 mm at day 7) carries clearer clinical relevance, as reduced probing depths at the distal aspect of the second molar have implications for long-term periodontal health of the adjacent tooth.

The present study has certain limitations. The relatively small sample size ($n = 42$) and short follow-up of 14 days limit the generalizability of findings and preclude assessment of long-term bone regeneration and periodontal outcomes. Swelling was quantified by facial measurements rather than volumetric analysis, and pain was assessed using the subjective VAS scale, both of which may introduce measurement variability. Additionally, growth factor concentrations (PDGF, TGF- β , VEGF) were not assayed, limiting mechanistic interpretation of the observed clinical differences.

A limitation of this split-mouth study is the inability to blind the operator during socket treatment, which may have introduced procedural bias. Additionally, variations in the timing of I-PRF application before polymerisation could have affected treatment consistency.

In summary, the findings of the present study suggest that I-PRF confers a clinically and statistically meaningful advantage over conventional PRF in early postoperative wound healing following mandibular third molar surgery. The biological basis for this advantage lies in its superior cellular viability, uniform intrasocket diffusion, and sustained growth factor bioavailability. However, the convergence of outcomes by day 7 for pain and the modest absolute difference in healing scores underscore that both materials achieve satisfactory clinical outcomes and that I-PRF's principal benefit is in accelerating the early inflammatory-to-proliferative transition. Future randomised controlled trials with larger sample sizes, longer follow-up, quantitative growth factor assays, and blinded outcome assessment are warranted to consolidate these findings.

Limitations:

The limitations of this study include a small sample size, a short follow-up duration, and its conduct at a single centre. In addition, healing was evaluated only through clinical assessment, without radiographic or histological analysis. The possibility of observer bias cannot be completely excluded.

CONCLUSION

I-PRF demonstrated favourable postoperative healing in contrast to PRF in this study. Increased penetration into the extraction socket, enriched concentration of growth factors, and regenerative cell constituents. In contrast to a solid PRF membrane, the slow development of a natural fibrin scaffold further stimulates early tissue regeneration, angiogenesis, and collagen formation, facilitating enhanced and effective healing.

DECLARATION

Conflict of Interest

The author declares no conflict of interest.

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Ethical approval

The study was reviewed by the College Ethical Committee.

Consent for publication

Patients were informed verbally and in writing about the study and gave written informed consent.

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ORIGINAL ARTICLE

ORAL HEALTH STATUS OF PRESCHOOL CHILDREN WITH RECURRENT UPPER RESPIRATORY TRACT INFECTIONS

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ABSTRACT

Background: The adverse social, educational, and economic consequences of recurrent respiratory tract infections have led to increased attention from healthcare professionals to this problem. The aim of this study was to assess the level of oral health and the factors of local nonspecific defense in children with recurrent upper respiratory tract infections.

Materials and Methods: The oral health status of 52 preschool children with recurrent upper respiratory tract infections (RRIs) and 35 healthy peers was evaluated. Caries indices (dmf, dmfs, DMF, DMFS), oral hygiene indices (Stallard, Silness–Löe), periodontal indices (PMA%, bleeding index, Schiller–Pisarev test), the confidence interval of oral fluid pH fluctuations, and its biochemical parameters (catalase activity, malondialdehyde, lysozyme, urease, and elastase) were determined.

Results: In children with RRIs, a decrease in the level of oral health to 66.7% was observed, attributable to the high prevalence of dental caries and gingivitis. A weakening of the nonspecific defense factors of oral fluid was also identified, characterized by an unstable pH state, decreased catalase activity ($p < 0.001$) and lysozyme activity ($p < 0.001$), and increased concentrations of malondialdehyde ($p < 0.001$), urease ($p < 0.001$), and elastase.

Conclusion: High caries prevalence, unfavorable oral hygiene and periodontal indices, and weakened local nonspecific defense mechanisms in children with RRIs necessitate the development of targeted therapeutic and preventive measures.

Keywords: dental health, nonspecific resistance, recurrent respiratory tract infections, children

INTRODUCTION

Recurrent respiratory tract infections (RRIs) represent repeated cases of acute respiratory infections with a high frequency of episodes (eight or more per year). The adverse social, educational, and economic consequences of RRIs determine the increased attention

of medical professionals to this problem^{1–3}. The proportion of RRIs of the upper respiratory tract in various age groups ranges from 4.0–18.0% to 27.0–40.0%, with the most consistently high level observed in the preschool child population⁴. The predisposition

of preschool children to RRI is a result of the physiological immaturity of both systemic and local immunity⁵⁻⁶.

In children with frequent year-round episodes of acute infections of the upper respiratory tract, significant alterations in the microbiome of the oral cavity and upper airways have been identified⁷⁻⁸. There is evidence that children with RRI exhibit a low level of oral hygiene and an increased progression of dental caries affecting both primary and permanent dentitions⁹⁻¹¹. The 20-year prospective Espoo Cohort Study established that frequent acute upper respiratory tract infections in early childhood were predictors of a higher prevalence of dental caries in permanent teeth during adulthood¹². Also, from a public health perspective, research demonstrating the impact of early childhood caries on the increased frequency of acute respiratory infection episodes in children is highly significant¹³⁻¹⁵. Furthermore, it was established that in young adults aged 20–27 years, the risk of lower respiratory tract diseases increased in proportion to the number of filled teeth, reaching its peak in individuals with ten or more filled teeth¹⁶.

However, a literature analysis has revealed that over the past 10 years, only a small number of publications have been dedicated to the dental problems of children with RRI.

The oral cavity serves as the entry point for microbial agents into the human body, and the protective mechanisms of saliva constitute one of the first barriers encountered by respiratory pathogens¹⁷. Therefore, studying the state of the nonspecific protective factors of the oral cavity in children with RRI is of significant interest. Research in this direction may assist in the development of therapeutic and preventive measures aimed at improving the quality of both oral and respiratory health in children.

The study was aimed at assessing the level of dental health and the factors of local nonspecific defense in children with RRI of the upper respiratory tract.

MATERIALS AND METHODS

An analytical comparative cross-sectional study was conducted involving 52 children with recurrent respiratory tract infections (RRI) (the main group), including 29 (55.8%) boys and 23 (44.2%) girls, and 35 apparently healthy children (the control group), including 19 (54.3%) boys and 16 (45.7%) girls. No formal sample size calculation was performed; the

sample size was determined by the number of eligible participants available during the study period.

To be included in the study, a child had to meet the following criteria: age 6–7 years, absence of hereditary or systemic chronic diseases, no acute respiratory infections within the previous month, no use of antibiotics or nonsteroidal anti-inflammatory drugs within the previous month, no regular medication intake, and willingness to cooperate.

The children included in the study were from families with a moderate socioeconomic status, assessed according to indicators such as household income and parental educational level.

A mandatory requirement for participation was obtaining voluntary written informed consent from parents or legal guardians. The study was carried out in accordance with ethical principles, including the World Medical Association Declaration of Helsinki.

The clinical examination was performed in the dental office of the Municipal Budgetary Educational Institution “Secondary General Education School – Combined Kindergarten No. 6” in Simferopol. Information regarding episodes of RRI was obtained from medical records and additionally through questionnaires completed by parents.

The Infectious Index (II) was calculated as the ratio of the total number of acute respiratory infection episodes over one year to the child’s age. The Resistance Index (RI) was calculated as the ratio of the number of acute respiratory infection episodes to the number of months of observation.

During the dental examination, the following parameters were assessed: dental caries indices (dmf, dmfs, DMF, DMFS), oral hygiene status using the Silness–Löe and K. Stallard indices, and periodontal condition using the PMA%, bleeding index, and Schiller–Pisarev test. Based on these findings, the Dental Health Level (DHL) was calculated as a percentage. The assessment was based on numerical health indicators defined for nine groups of dental diseases [18]. The DHL value depends on the severity of the pathology, the degree of impairment of masticatory function, and the extent of required therapeutic interventions.

To assess the acid–base status of oral fluid, pH measurements were performed on three samples using a portable pH meter/millivoltmeter pH-410.

The arithmetic mean of the values was calculated, after which the confidence interval of deviation (ΔpH) from the mean value was determined using the following formula:

$$\Delta pH = t_{3;0.95} \sqrt{\sum_{i=1}^3 (\Delta pHi)^2 / 3(3-1)}, \text{ where}$$

$t_{3;0.95}$ was Student's coefficient with a 0.95 confidence probability for three measurements;

ΔpHi was the deviation of the pHi values from the arithmetic mean.

This calculation was performed after a preliminary graphical analysis to evaluate whether the data could be approximated by a normal distribution. A biochemical analysis of mixed saliva was performed in 31 children with RRI (study group) and 21 healthy children (control group). Oral fluid was collected in the morning into sterile tubes using the spitting method. The children had not eaten breakfast and had not performed morning oral hygiene. The samples were stored at -20°C . After thawing, they were centrifuged for 15 minutes at 3,500 rpm, after which biochemical analyses were performed. Elastase activity in oral fluid was determined spectrophotometrically at a wavelength of 347 nm. The method is based on the hydrolysis of the synthetic substrate Boc-L-alanine-p-nitrophenyl ester by the enzyme, resulting in the formation of yellow p-nitrophenol. One katal was defined as the amount of enzyme activity that catalyzes the formation of one mole of p-nitrophenol ¹⁹. Catalase activity was measured photometrically at a wavelength of 410 nm. The method is based on the ability of ammonium molybdate to form a yellow-colored complex upon reaction with hydrogen peroxide. One unit of catalase activity was defined as the amount of enzyme that catalyzes the decomposition of one mole of hydrogen peroxide ¹⁹.

The concentration of malondialdehyde (MDA) in oral fluid was determined photometrically at a wavelength of 530 nm using the thiobarbituric acid method ¹⁹. Lysozyme activity in oral fluid was measured spectrophotometrically at a wavelength of 540 nm (after 15 and 180 minutes) using the indicator culture *Micrococcus lysodeikticus* ATCC 4698 ²⁰. Urease activity was determined based on the enzymatic breakdown of urea into ammonia, which reacts with Nessler's reagent, producing a yellow color. Urease activity was expressed in micromoles of ammonia formed per minute per liter of oral fluid. Optical density was measured using an SF-56 spectrophotometer. The degree of dysbiosis (DD) was calculated as the ratio of specific urease activity to specific lysozyme activity ²⁰.

Biochemical analyses were performed at the "Molecular Biology" Core Facility of the Central Research Laboratory at the Order of the Red Banner of Labour Medical Institute named after S. I. Georgievsky. During statistical analysis, the arithmetic mean, standard error, median (Me), and lower (Q1) and upper (Q3) quartiles were calculated. Statistical analysis included assessment of data distribution using graphical methods (histograms and comparison with a theoretical normal distribution curve), as well as evaluation of skewness and kurtosis. In addition, the one-sample Kolmogorov–Smirnov test was used to test the hypothesis that the data could be approximated by a normal distribution. Based on graphical analysis, parametric statistical methods were considered appropriate in most cases, which justified the use of confidence intervals and Student's t-test. However, given the relatively small sample sizes, non-parametric methods were also applied to assess differences between groups. The Mann–Whitney U test was used as a non-parametric alternative to the independent samples t-test. Z values, asymptotic two-sided significance, and exact significance values were calculated. The two-sample Kolmogorov–Smirnov test was also used to assess differences in distribution shape. For small samples ($n \leq 30$), exact p-values were used instead of asymptotic ones. The level of statistical significance was set at $\alpha = 0.05$. Differences between groups were assessed using Student's t-test for normally distributed data with equal variances. When these assumptions were not met, the Mann–Whitney U test was applied. Statistical analysis was performed using Microsoft Excel 2024 (Microsoft, USA). Further statistical processing was carried out using the R statistical computing environment. The packages stats, ctest, FactoMineR, and others were used. R is a free and open-source software environment for statistical computing developed under the GNU Project.

RESULTS

The analysis of medical documentation revealed significant differences in the Infectious Index (II) and Resistance Index (RI) between the groups: the II in the study group was 1.23 ± 0.04 , compared to 0.29 ± 0.02 in the control group ($p < 0.001$); the RI was 0.61 ± 0.02 and 0.15 ± 0.018 ($p < 0.001$), respectively. The clinical examination identified a large number of filled and decayed primary teeth in 50 (96.15%) children with RRI. The dmfi index was 5.9 ± 0.45 , and dmfs was 6.3 ± 0.56 ($p < 0.001$). Additionally, carious lesions in the fissures and cervical areas of the first permanent molars were frequently diagnosed. The DMFI index was 1.25 ± 0.03 , and DMFS was 1.45 ± 0.02 ($p < 0.001$).

The prevalence of dental caries in primary teeth among children in the control group was 82.8% (29 individuals), with lower caries intensity indices (dmf was 3.35 ± 0.41 , dmfs – 3.51 ± 0.45). The intensity of caries in permanent teeth, according to the indices, was as follows: DMF – 0.43 ± 0.11 , DMFS – 0.51 ± 0.13 . Chronic catarrhal gingivitis was diagnosed in 46 children with RRI (88.5% of cases), compared with 13 individuals (37.1%) in the control group. Significant differences were observed in the indices characterizing periodontal status. In the main group, the PMA index reached $22.9 \pm 1.6\%$ ($p < 0.001$), and the bleeding index was 0.19 ± 0.03 points ($p < 0.05$). Oral hygiene indices in children with RRI were significantly worse than in the control group, with the Silness–Löe index being 1.9 ± 0.08 points ($p < 0.001$) and the K. Stallard index being 2.05 ± 0.08 points ($p < 0.01$). Based on the clinical examination results, the Dental Health Level (DHL) in children with RRI was reduced to 66.7% (compared with 84.6% in the control group). The reduction in DHL in this group was primarily associated with a high intensity of untreated caries and a large number of primary teeth affected by complicated caries. The results of the biochemical analysis of oral fluid in children with RRI are summarized in Table 1.

Table 1. Biochemical parameters of oral fluid in children with recurrent respiratory infections (Me (Q1; Q3))

Indicator	Study group n=31	Control group n=21	Significance of differences between groups
Catalase, mkat/L	0,101 [0,092; 0,111]	0,255 [0,221; 0,261]	$p=0.000076^*$
MDA, mmol/L	0,45 [0,40; 0,52]	0,17 [0,13; 0,20]	$p=0.002438^*$
Lysozyme, units/L	51,4 [47,3; 57,3]	76,2 [7,7; 85,4]	$p=0.008614^*$
Urease, μ kat/L	0,850 [0,742; 0,912]	0,206 [0,172; 0,219]	$p=0.000001^*$
Elastase, μ kat/L	2,45 [1,87; 3,10]	2,19 [1,72; 2,34]	$p=0.597439$

*Statistically significant differences at $p < 0.05$

Catalase activity in the oral fluid of children with RRI was significantly lower than in the control group ($p < 0.001$). A statistically significant increase in malondialdehyde (MDA) concentration was observed in children of the main group compared with controls ($p < 0.001$), indicating the development of oxidative stress and a reduced capacity of the antioxidant system to counteract lipid peroxidation.

In the oral fluid of children with RRI, urease activity—a marker of microbial load—was increased,

on average four times higher than in healthy peers, suggesting enhanced colonization of the oral cavity by opportunistic and pathogenic microorganisms. At the same time, a 1.5-fold decrease ($p < 0.001$) in lysozyme concentration was observed, indicating weakening of local antimicrobial defense mechanisms.

The disruption of the oral microbiota profile in the main group was further confirmed by an increase in the dysbiosis degree (DD) index to 2.95, which was approximately two times higher than in the control group (DD = 1.44) and 2.9 times higher than the reference “normal” value of 1. Against this background, increased elastase activity, a marker of inflammation, was detected in the main group. It should be noted that even in the control group, elastase levels in oral fluid exceeded normative values, which may be explained by the presence of mild inflammatory changes in gingival tissues associated with suboptimal oral hygiene, including edema, hyperemia, and bleeding.

Children with RRI exhibited disturbances in the acid–base balance of the oral cavity. The confidence interval of hydrogen ion fluctuations (Δ pH) in mixed saliva was 1.9 times higher than in the control group, amounting to 0.27 ± 0.02 ($p < 0.001$). A stable pH of oral fluid is a crucial component of oral homeostasis. Its disturbance in children with RRI represents a risk factor for dental caries in permanent teeth and gingivitis.

DISCUSSION

We set out to test the hypothesis that preschool children with recurrent respiratory tract infections (RRI) have a deterioration in oral health status and in local protective mechanisms. The results of our study revealed higher levels of dental caries in both primary and permanent teeth in these children compared with their healthy peers. These findings are consistent with those of other authors who have shown that children with RRI are more susceptible to dental caries than generally healthy individuals^{9,21}.

Kaskova L.F. and co-authors associate this with the development of a cariogenic situation in the oral cavity, including a reduction in the structural and functional resistance of enamel, poor oral hygiene, and disturbances in the composition and properties of oral fluid^{10, 22}.

Information on the direct correlation between early childhood caries and the frequency of acute upper respiratory tract infections across different age groups is of significant importance for public health practice^{13, 14, 15}. Therefore, the relationship between RRIs and the condition of the oral cavity appears to be bidirectional.

Frequent episodes of acute respiratory infections alter the structure of the oral microbiocenosis⁸. During acute respiratory diseases, there is a reduction in the relative abundance of microorganisms typical for this ecological niche, alongside an increase in opportunistic flora (such as *Staphylococcus aureus*, β -hemolytic streptococci, and others) and colonization by microorganisms not typical for the oral cavity²³.

As a result of frequent respiratory infections, local immunity is suppressed, which contributes to the development of oral dysbiosis^{5,6}. Continuous antigenic stimulation and inflammatory processes lead to changes in the composition and properties of saliva. A decrease in the levels of lysozyme, lactoferrin, and specific antibodies (sIgA) in oral fluid during respiratory illness weakens the control over pathogenic microorganisms, allowing them to dominate the biotope. A reduction in the anti-adhesive activity of saliva in adolescents with RRIs, even during periods of clinical well-being, has been demonstrated in the study by Generalova E.V. (2023)²⁴. It is known that the anti-adhesive properties of saliva integrally reflect the function of key components of local defense, such as secretory immunoglobulin A, lysozyme, lactoferrin, and others. Our study demonstrated suppression of lysozyme activity and increased urease activity in mixed saliva in children with RRIs.

Acute respiratory infections are also the main reason for prescribing antibiotics and anti-inflammatory drugs²⁵. These medications negatively affect oral fluid homeostasis and microbial balance. Their frequent use leads to the elimination of beneficial commensals such as *Streptococcus salivarius* and creates ecological niches for the growth of opportunistic fungi (for example, species of the genus *Candida*) and Gram-negative bacteria. For instance, it has been shown that children with RRIs exhibit a significant increase in the adhesion index of *Candida albicans* to a single buccal

epithelial cell. A correlation was observed between microbiota composition, the activity of the inflammatory process in the oral and gastrointestinal mucosa, and the severity of tissue involvement⁷. Dysbiosis of the oral microbiome increases colonization of the oral cavity by opportunistic and pathogenic microorganisms, which may subsequently enter the upper and lower respiratory tract, leading to respiratory diseases. In turn, these diseases may further destabilize the oral microbiota balance. This creates a vicious cycle that contributes to the deterioration of both oral and respiratory health²⁶.

An imbalance in the oral and nasopharyngeal microecology leads to the development of oxidative stress and inflammation. In our study, this was confirmed by increased lipid peroxidation (as indicated by malondialdehyde levels), increased activity of the proteolytic enzyme elastase, and decreased activity of the antioxidant enzyme catalase.

However, when interpreting the results of this study, several limitations should be considered. The relatively small sample size and single-center design may limit the generalizability of the findings. In addition, potentially important influencing factors were not assessed, including dietary habits, oral hygiene practices, fluoride exposure, and prior antibiotic use. Future multicenter longitudinal studies with larger sample sizes are needed to confirm these findings and further clarify the relationship between recurrent respiratory infections and oral health status in children.

CONCLUSION

A low level of oral health (66.7%) was identified in children with RRIs. The high prevalence and intensity of dental caries, together with the severity of gingival inflammation and weakened local nonspecific defense factors, highlight the need for the development of targeted therapeutic and preventive measures aimed at improving oral health.

Authors' Contributions

All authors contributed substantially to the work presented and gave final approval of the version for publication. Kolesnik K.A.: Conceptualization, Methodology, Writing—review and editing. Romanenko I.G.: Supervision. Dzhemileva L.E.: Investigation, Writing—original draft. Severinova S.K.: Investigation. Sadikov A.R.: Investigation, Formal analysis.

DECLARATIONS

Conflict of Interest

The authors declare no conflict of interest.

Funding

No external funding was received for this study.

Ethical approval

The study was reviewed and approved by University Ethical Committee (and in accordance with those of the World Medical Association and the Helsinki Declaration.

Consent for publication

Patients were informed verbally and in writing about the study and gave written informed consent.

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ORIGINAL ARTICLE

APPLICATION OF INJECTABLE AND SOLID PLATELET-RICH FIBRIN (IPRF AND SPRF) IN RHINOPLASTY WITHIN THE CONCEPT OF LOW SPEED, HORIZONTAL CENTRIFUGATION WITH LOW CENTRIFUGAL FORCE (LSHCC).

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Abstract

Background: Achieving stable graft integration and smooth nasal contour remains a major challenge in rhinoplasty, particularly in patients with thin nasal skin and in revision procedures. Platelet-rich fibrin (PRF), prepared according to the low-speed horizontal centrifugation concept (LSHCC), represents a fully autologous biomaterial that combines regenerative potential with mechanical support. This study evaluated the clinical effectiveness of injectable platelet-rich fibrin (I-PRF) and solid platelet-rich fibrin (S-PRF) as adjuncts for diced cartilage grafting and soft-tissue camouflage in rhinoplasty.

Methods: A prospective observational clinical study included 1,568 consecutive patients who underwent primary or revision rhinoplasty between September 2009 and November 2025. PRF was prepared using horizontal centrifugation at 1000 rpm for 8 minutes (approximately 200 × g). Injectable PRF was mixed with finely diced autologous cartilage, whereas solid PRF membranes were used for graft stabilization, dorsal and tip camouflage, and soft-tissue regeneration. Clinical outcomes included contour smoothness, graft stability, wound healing, complications, revision rate, and patient satisfaction during a 12-month follow-up.

Results: Among the patients, 1,320 (84.2%) underwent primary and 248 (15.8%) revision rhinoplasty. Septal cartilage was used in 1,333 (85%) cases and costal cartilage in 235 (15%). Excellent or good aesthetic outcomes were achieved in 1,396 patients (89%). Stable graft positioning and smooth dorsal contour were maintained in 1,537 patients (98%), with no clinically significant graft resorption. S-PRF eliminated the need for fascia or perichondrial graft harvesting in 100% of cases. Septal mucosal defects in 110 patients were successfully repaired with PRF membranes without postoperative perforation. No infections, hematomas, skin necrosis, allergic reactions, foreign-body reactions, or graft extrusion occurred. Minor contour irregularities requiring correction developed in 31 patients (2%), while clinically significant graft displacement occurred in only 2 patients (0.15%). No revision surgery related to PRF-treated grafts was required. Mean patient satisfaction was $9.0 \pm 0.62/10$, with 98% of patients reporting satisfaction or high satisfaction.

Conclusions: Injectable and solid PRF prepared according to the LSHCC protocol appear to be safe and effective biological adjuncts in rhinoplasty. PRF enhances graft stabilization, improves soft-tissue healing, eliminates the need for additional fascial grafts, and provides excellent aesthetic outcomes with an exceptionally low complication rate. Further controlled comparative studies with longer follow-up are warranted.

Keywords: Rhinoplasty; platelet-rich fibrin; injectable platelet-rich fibrin; diced cartilage; regenerative rhinoplasty; low-speed centrifugation; horizontal centrifugation; autologous grafts.

INTRODUCTION

Rhinoplasty is one of the most frequently performed procedures in facial plastic surgery and remains one of the most technically demanding operations^{1,2}. Besides improving facial appearance, successful rhinoplasty

requires preservation or restoration of normal nasal function. Despite continuous advances in surgical techniques, obtaining a smooth, natural, and stable nasal contour is still challenging, particularly in patients with thin skin, post-traumatic deformities, or those undergoing revision surgery. Even small postoperative

irregularities or graft visibility may compromise the final aesthetic result and reduce patient satisfaction³⁻⁵.

Autologous cartilage remains the preferred grafting material because of its excellent biocompatibility, low immunogenicity, and long-term stability^{6,7}. Septal cartilage is usually the first choice, whereas auricular and costal cartilage are used when additional graft material is required⁸⁻¹¹. Nevertheless, conventional cartilage grafts have several well-recognized limitations. Graft visibility, palpability, contour irregularities, warping, and partial resorption may occur, especially in thin-skinned patients and in revision rhinoplasty^{12,13}.

To improve contour refinement, diced cartilage has become an established alternative to solid cartilage grafts^{14,15}. Because of its flexibility, finely diced cartilage adapts well to the underlying nasal framework and provides smoother contour transitions. However, successful use of diced cartilage depends on reliable stabilization after implantation. Without adequate support, cartilage particles may migrate, disperse, or undergo unpredictable resorption¹⁶. For this reason, various wrapping materials, including fascia, perichondrium and other biological substitutes, have been introduced over the years¹⁶⁻²¹.

Although fascia-wrapped diced cartilage has shown good long-term clinical results, harvesting fascia requires an additional donor site, prolongs the operation, and increases patient morbidity. This has encouraged surgeons to search for autologous materials that can simultaneously stabilize cartilage grafts and improve tissue healing without creating additional surgical trauma¹⁶⁻²¹.

Platelet-rich fibrin (PRF) has attracted considerable interest in regenerative medicine during the past decade. Unlike platelet-rich plasma (PRP), PRF is prepared without anticoagulants, allowing natural coagulation to produce a fibrin matrix rich in platelets, leukocytes, cytokines, and growth factors. This matrix gradually releases biologically active molecules that promote angiogenesis, collagen synthesis, cell migration, and tissue remodeling during wound healing^{22,23}.

The biological properties of PRF depend largely on the centrifugation protocol. Experimental studies have shown that reducing the relative centrifugal force preserves a greater number of platelets and regenerative cells within the fibrin clot, resulting in enhanced biological activity. More recently, horizontal centrifugation has been introduced to improve the separation of blood components and achieve a more

homogeneous distribution of regenerative cells throughout the PRF matrix^{24,25}.

Both injectable platelet-rich fibrin (I-PRF) and solid platelet-rich fibrin (S-PRF) have recently been introduced into reconstructive and aesthetic surgery. Injectable PRF can be mixed with diced cartilage to create a cohesive graft, whereas compressed S-PRF membranes provide mechanical support while serving as a biologically active scaffold. These complementary characteristics have expanded the clinical use of PRF from oral and maxillofacial surgery to several other surgical specialties, including facial plastic surgery²⁶⁻²⁹.

In rhinoplasty, the combination of I-PRF, diced cartilage, and S-PRF membrane offers a regenerative approach that addresses both graft stabilization and soft-tissue healing. Experimental studies have demonstrated improved cartilage regeneration and chondrocyte viability with I-PRF compared with conventional PRP, while early clinical reports suggest reduced postoperative edema, improved graft integration, and decreased donor-site morbidity³⁰⁻³². However, clinical evidence remains limited, particularly regarding standardized preparation protocols and long-term outcomes.

The aim of the present study was to evaluate the clinical application of injectable and solid platelet-rich fibrin prepared according to the low-speed horizontal centrifugation concept (LSHCC) in primary and revision rhinoplasty. We assessed its role in stabilizing diced cartilage grafts, improving contour camouflage, enhancing soft-tissue healing, and reducing the need for additional donor tissues.

2. MATERIALS AND METHODS

2.1 Study Design and Ethical Approval

This prospective clinical study was designed to evaluate the clinical performance of injectable platelet-rich fibrin (I-PRF) and solid platelet-rich fibrin (S-PRF), prepared according to the Low-Speed Horizontal Centrifugation Concept (LSHCC), as biological adjuncts in primary and revision rhinoplasty. The study included consecutive patients who underwent rhinoplasty at the Department Aesthetic and Maxillofacial Surgery, Erebouni Medical Center, Yerevan, Armenia between September 2009 and November 2025.

All surgical procedures were performed by the same surgical team using a standardized operative protocol. Clinical data were collected prospectively and included patient demographics, operative findings, graft characteristics, postoperative healing, complications, and patient-reported outcomes.

All participants provided written informed consent before surgery, including consent for clinical photography and the anonymous use of their data for scientific publication.

2.2 Patient Population

A total of 1,568 consecutive adult patients were enrolled during the study period. Patients were eligible if they were 18 years of age or older, underwent either primary or revision rhinoplasty, and required cartilage grafting combined with PRF-assisted reconstruction for dorsal augmentation, contour camouflage, supratip refinement, tip refinement, or correction of minor surface irregularities.

Patients were excluded if they had active local or systemic infection, coagulation disorders, thrombocytopenia or platelet dysfunction, were receiving anticoagulant therapy, had uncontrolled diabetes mellitus, autoimmune diseases known to interfere with wound healing, were pregnant or breastfeeding, or declined participation in the study.

Of the 1,568 patients, 1,500 (95.7%) were women and 68 (4.3%) were men. The mean patient age was 22 ± 1.6 years (range, 18–45 years). Primary rhinoplasty was performed in 1,320 patients (84.2%), whereas 248 patients (15.8%) underwent revision surgery.

Autologous septal cartilage was used whenever sufficient graft material was available and was harvested in 1,333 patients (85.0%). Costal cartilage was required in 235 patients (15.0%), mainly in revision procedures and complex structural reconstructions. Auricular cartilage was not used in this series.

Injectable PRF (I-PRF) combined with finely diced cartilage was used in all patients. Depending on the intraoperative findings, solid PRF (S-PRF) membranes were applied for dorsal camouflage, stabilization of diced cartilage grafts, supratip contouring, tip refinement, alar dome camouflage, coverage of structural cartilage grafts, or repair of intraoperative septal mucosal defects.

The mean postoperative follow-up period was 12 ± 6 months (range, 12–24 months). Demographic and clinical characteristics of the study population are presented in Table 1.

Table 1. Baseline demographic and clinical characteristics of the study population

Characteristic	Value
Total number of patients	1,568
Age, years (mean ± SD)	22 ± 1.6
Age range, years	18–45
Female, n (%)	1,500 (95.7)
Male, n (%)	68 (4.3)
Primary rhinoplasty, n (%)	1,320 (84.2)
Revision rhinoplasty, n (%)	248 (15.8)
Septal cartilage graft, n (%)	1,333 (85.0)
Costal cartilage graft, n (%)	235 (15.0)
Auricular cartilage graft, n (%)	0 (0)
I-PRF used, n (%)	1,568 (100)
S-PRF membrane applied*	According to the surgical indication
Mean follow-up, months (mean ± SD)	12 ± 6
Follow-up range, months	12–24

*Solid platelet-rich fibrin membranes were used for dorsal camouflage, stabilization of diced cartilage grafts, tip refinement, supratip contouring, alar dome camouflage, coverage of cartilage grafts, and repair of septal mucosal defects whenever clinically indicated.

2.3 Preparation of Platelet-Rich Fibrin

Autologous platelet-rich fibrin was prepared immediately before surgery under sterile operating room conditions. Peripheral venous blood was collected from each patient immediately prior to rhinoplasty without the use of anticoagulants.

Preparation of both injectable PRF (I-PRF) and solid PRF (S-PRF) followed the Low-Speed Horizontal Centrifugation Concept (LSHCC), which has been shown to preserve a greater proportion of platelets, leukocytes, and regenerative cells within the fibrin matrix compared with conventional high-speed centrifugation protocols.

Blood samples were centrifuged horizontally at 1000 rpm for 8 minutes, corresponding to an approximate relative centrifugal force (RCF) of 200 × g. Solid PRF membranes were prepared using sterile glass tubes without anticoagulants, whereas I-PRF was obtained from sterile plastic tubes specifically intended for liquid PRF preparation.

Following centrifugation, the fibrin clot designated for S-PRF was gently separated from the red blood cell layer and compressed to produce a uniform membrane suitable for graft coverage and stabilization. Injectable PRF was aspirated immediately after centrifugation while still in its liquid phase and was promptly mixed with finely diced autologous cartilage before coagulation.

To preserve the biological activity of platelets, leukocytes, cytokines, and growth factors, both PRF formulations were prepared immediately before implantation and used without delay during the surgical procedure.

2.4 Surgical Technique

All rhinoplasty procedures were performed by the same experienced surgeon using a standardized surgical approach. The operative technique was selected according to the individual anatomical characteristics of each patient, including primary or revision status, skin thickness, nasal deformity, and reconstructive requirements.

An open rhinoplasty approach was performed through a transcolumellar incision when extensive structural modification or graft placement was required. After elevation of the skin–soft tissue envelope, standard nasal framework modifications were carried out, including dorsal refinement, tip reshaping, correction of asymmetries, and placement of cartilage grafts when indicated. Following completion of the structural rhinoplasty procedure, PRF preparations were applied according to the predefined protocol. Injectable platelet-rich fibrin (IPRF) was administered into targeted soft tissue planes, including the nasal dorsum, supratip region, tip area, and areas with potential postoperative fibrosis or contour irregularities. Solid platelet-rich fibrin (SPRF) membranes were positioned as biological support materials in selected cases, particularly around cartilage grafts and areas requiring enhanced soft tissue healing and contour stabilization.

The PRF application was performed after preparation of the final nasal framework and before closure of the surgical incision. The nasal skin envelope was repositioned carefully, and the incision was closed using standard surgical techniques. External nasal splinting and postoperative dressing were applied according to routine rhinoplasty protocols.

2.5 Postoperative Follow-up

Patients were followed prospectively after surgery according to a standardized postoperative evaluation schedule. Clinical examinations were performed at predefined time points: postoperative day 7, 1 month, 3 months, 6 months, and 12 months.

During follow-up visits, patients were evaluated for postoperative healing, edema resolution, skin–soft tissue adaptation, nasal contour changes, and possible complications. Particular attention was given to supratip fullness, dorsal irregularities, contour smoothness, graft visibility, and symmetry.

Standardized clinical photographs were obtained during follow-up visits using consistent photographic conditions and nasal views, including frontal, lateral, and oblique perspectives. Postoperative outcomes were assessed by comparing serial clinical findings and photographic documentation.

Any adverse events, including infection, hematoma, prolonged edema, fibrosis, graft-related complications, or need for revision surgery, were recorded.

2.6 Outcome Measures

The primary outcome was the evaluation of the effect of PRF application on postoperative nasal contour quality and soft tissue healing following rhinoplasty.

Secondary outcomes included:

- reduction of postoperative edema duration;
- improvement of nasal skin–soft tissue adaptation;
- prevention or reduction of contour irregularities;
- enhancement of graft integration and stability;
- incidence of postoperative fibrosis or scar-related deformities;
- patient satisfaction with aesthetic outcomes.

Clinical outcome assessment was performed using standardized photographic evaluation and surgeon-based clinical scoring. Patient-reported satisfaction was assessed using a structured postoperative questionnaire evaluating overall aesthetic appearance, nasal shape, and functional satisfaction.

Postoperative complications and revision procedures were also analyzed as safety outcomes.

2. Statistical Analysis

Statistical analysis was performed using appropriate statistical software. Continuous data were expressed as mean ± standard deviation or median with interquartile range, according to data distribution. Categorical variables were presented as frequencies and percentages. Preoperative and postoperative results were compared using appropriate paired statistical tests. Categorical variables were analyzed using chi-square or Fisher’s exact test when required. Changes during follow-up were evaluated using repeated measurements analysis or equivalent non-parametric methods. A p-value <0.05 was considered statistically significant.

3. RESULTS

A total of 1568 patients who underwent rhinoplasty with adjunctive application of injectable platelet-rich fibrin (IPRF) and solid platelet-rich fibrin (S-PRF) were included in the final analysis. Patients were followed according to the predefined postoperative protocol. Clinical evaluation demonstrated progressive soft-tissue adaptation, stable graft integration, and improvement of nasal contour during the follow-up period.

3.1 Surgical Outcomes

The combined application of injectable and solid platelet-rich fibrin demonstrated favorable effects on graft stabilization, soft-tissue adaptation, and postoperative contour refinement. Excellent or good aesthetic outcomes were achieved in 1396 patients (89%), while satisfactory improvement was observed in 172 patients (11%). Stable fixation of diced cartilage grafts without clinically detectable migration was maintained in 1537 patients (98%) throughout the follow-up period. Smooth dorsal contour and successful camouflage of minor surface irregularities were achieved in 1537 patients (98%), with particularly favorable results observed among patients with thin nasal skin and revision rhinoplasty cases. The use of S-PRF membranes provided biological coverage of graft material and eliminated the requirement for additional fascia or perichondrial harvesting in 1568 patients (100%), reducing additional donor-site morbidity. Intraoperative septal mucosal defects occurred in 110 patients. All defects were covered using S-PRF membranes, and no postoperative septal perforation was observed. Postoperative healing was uneventful in the majority of patients, with gradual reduction of edema and progressive improvement of nasal contour during follow-up. The postoperative clinical outcomes of all 1,568 patients included in the study are

summarized in Table 2, Figure 1, demonstrating high rates of satisfactory aesthetic outcomes and a low incidence of postoperative complications .

Table 2. Clinical outcomes of PRF-assisted rhinoplasty in 1568 patients

Clinical parameter	Outcome after IPRF and S-PRF-assisted rhinoplasty
Total number of patients	1568
Follow-up period	6–24 months
Improvement of postoperative edema	Reduced compared with conventional rhinoplasty protocols
Time to visible reduction of swelling	Earlier postoperative soft tissue stabilization
Postoperative ecchymosis	Reduced severity and shorter duration
Soft tissue healing	Accelerated healing response with improved tissue quality
Skin–soft tissue envelope adaptation	Improved adaptation, particularly in thin-skinned patients
Graft integration/stability	Enhanced graft integration and contour stability
Dorsal and tip contour refinement	Improved smoothness of nasal contour
Revision requirement	Low incidence during follow-up
Postoperative infection	No clinically significant increase observed
Major complications	Rare
Patient satisfaction	High overall satisfaction reported

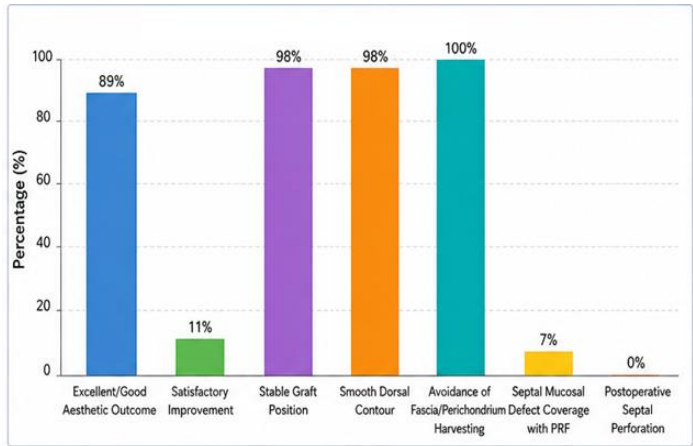


Figure 1. Surgical outcomes after rhinoplasty with IPRF and S-PRF application

3.2 Postoperative Complications

No major intraoperative or postoperative complications directly associated with PRF application were observed. No cases of infection, hematoma, skin necrosis, allergic reaction, foreign-body reaction, or graft extrusion were recorded during follow-up.

Minor contour irregularities requiring conservative or limited correction occurred in 31 patients (2%). Clinically significant graft displacement was identified in 2 patients (0.15%). No cases of partial graft resorption or revision surgery due to contour deformity were observed. No adverse events related to blood collection or PRF preparation were noted. Figure 1 demonstrating postoperative complications.

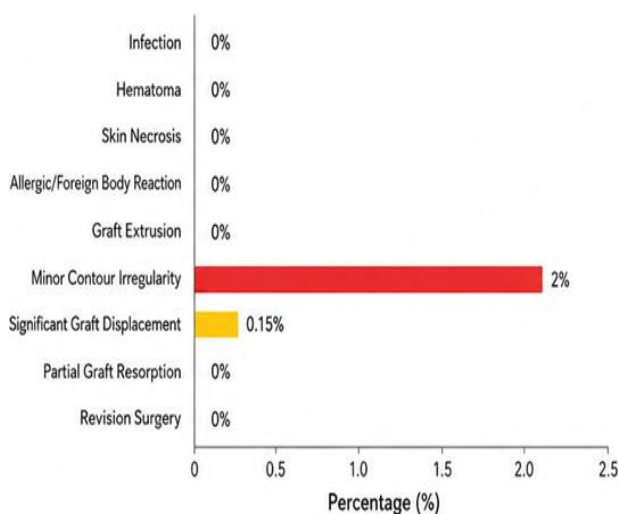


Figure 2. Postoperative complications

3.3 Patient Satisfaction and Surgeon-Based Evaluation

Patient-reported satisfaction was assessed at the final follow-up visit using a visual analogue scale (VAS, 0–10). The mean patient satisfaction score was 9.0 ± 0.62 .

A total of 1316 patients (84%) reported being very satisfied with the aesthetic outcome, while 219 patients (14%) were satisfied and 33 patients (2%) reported moderate satisfaction.

Patients most frequently reported satisfaction with:

- smooth dorsal contour;
- natural nasal appearance;
- reduced postoperative swelling;
- improved soft-tissue adaptation.

Surgeon-based aesthetic evaluation demonstrated

excellent or good outcomes in 1535 patients (97.9%), Figure 3.

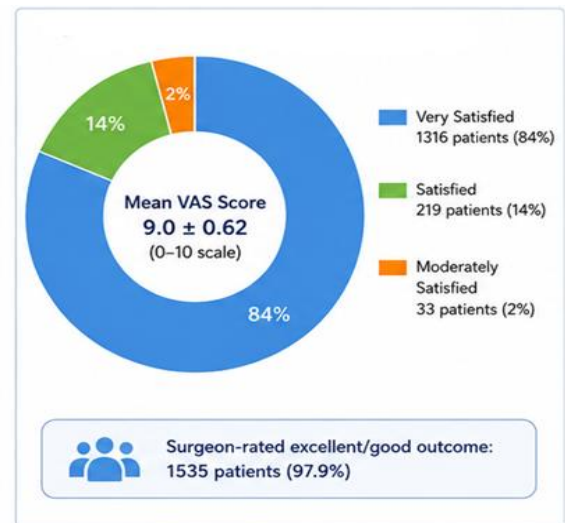


Figure 3. Patient, Surgeon-based satisfaction and aesthetic evaluation

Figure 4 demonstrating Overall Outcomes Summary.



Figure 4. Overall Outcomes Summary

3.4 Representative Clinical Case

A representative clinical case demonstrating the combined application of injectable platelet-rich fibrin (IPRF), solid platelet-rich fibrin (SPRF) membrane, and finely diced cartilage grafting is presented.

A female patient with thin nasal skin underwent primary rhinoplasty with aesthetic dorsal and tip refinement. After structural correction and cartilage harvesting, finely diced autologous cartilage was prepared and combined with injectable PRF concentrate (IPRF). The PRF-enriched diced cartilage mixture was used for dorsal contour refinement and camouflage of minor irregularities.

To stabilize the graft material and enhance soft-tissue adaptation, an SPRF membrane prepared according to

the low-speed centrifugation concept (LSCC) protocol was positioned over the treated area. The membrane acted as a biological stabilizing layer, reducing graft displacement and providing a favorable environment for graft integration.

Postoperative follow-up demonstrated progressive improvement of nasal contour, smooth dorsal transition, and preservation of graft position. No irregularities, graft visibility, or donor-site complications were observed during follow-up. Figure 5-9 demonstrating clinical case of rhinoplasty using PRF-assisted cartilage grafting.



Figure 5. a,b,c Preoperative frontal and lateral views demonstrating nasal contour deformity and thin soft-tissue .

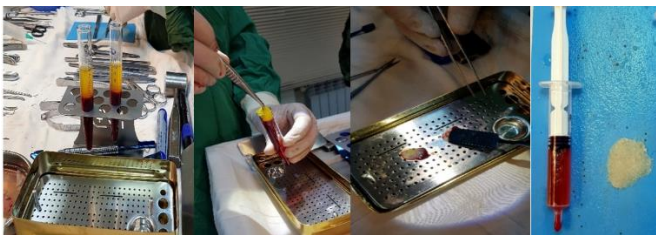


Figure 6.a,b,c,d Preparation of the PRF membrane using Choukroun set with LSCC protocol. Injectable IPRF concentrate and fine diced cartilage graft. The PRF membrane enriched with platelets and growth factors serves as a “fixator” for diced cartilage, preventing possible displacement while simultaneously promoting successful graft integration (fig. 7).



Figure 7.a,b,c Under the membrane placed in the area of the nasal tip. supratip area, or above the lateral crus of LLC, an insulin syringe containing finely diced

cartilage graft is used to inject this cartilage graft underneath the PRF membrane. The PRF membrane secures this autograft in the place where it should be, stabilizing it in that position and facilitating its better healing and integration.

At the same time, the use of SPRF membranes eliminates the need for harvesting other autologous grafts such as fascia or perichondrium, thereby avoiding the creation of new donor sites—particularly beneficial in primary rhinoplasty (fig. 8).



Figure 8. a,b,c PRF membrane allows (figures form left to the right) covering rigid cartilage autografts—tip grafts; covering nasal dorsum structures, helps to camouflage irregularities in the nasal dorsum in thin skin patient (or in revision rhinoplasties, in thinned skin patient); alar domes camouflage.



Figure 9.a,b,c Postoperative views demonstrating improved dorsal contour, smooth tip transition, and stable aesthetic outcome.

Furthermore, in cases of nasal septal mucosa perforations during surgery, where significant mucosal defects occur, this issue can be effectively resolved by applying PRF membranes. Their strong regenerative potential allows defect closure without resorting to additional donor sites or extensive mucosal flap elevation.

4. DISCUSSION

The present prospective clinical investigation examined the clinical applicability of injectable platelet-rich fibrin

(I-PRF) and solid platelet-rich fibrin (S-PRF), prepared according to the low-speed horizontal centrifugation concept (LSHCC), as autologous regenerative adjuncts in structural rhinoplasty. Rather than serving solely as biological fillers, these platelet concentrates were incorporated with the objective of combining the well-established structural reliability of cartilage grafting with the regenerative capacity of fibrin-based autologous biomaterials. While conventional rhinoplasty techniques primarily emphasize restoration of nasal framework and mechanical support through cartilage grafts, the addition of PRF is intended to optimize the biological environment surrounding the graft, thereby promoting tissue integration, physiological wound healing, and long-term maintenance of aesthetic outcomes. This concept reflects the ongoing transition in reconstructive surgery from purely structural reconstruction toward biologically guided tissue regeneration and tissue preservation^{2,3}.

The findings of the present study are based on a large prospective clinical series comprising 1,568 consecutive patients who underwent either primary or revision rhinoplasty between September 2009 and November 2025. Throughout this experience, the combination of finely diced autologous cartilage, injectable PRF, and solid PRF membranes yielded consistently favorable surgical and aesthetic outcomes. Injectable PRF was prepared using horizontal centrifugation at 1000 rpm for 8 minutes (approximately 200 × g) according to the principles of low-speed centrifugation, a protocol designed to maximize preservation of platelets, leukocytes, and regenerative mediators within the fibrin matrix^{24,28,30}. After preparation, I-PRF was thoroughly mixed with diced autologous cartilage to generate a cohesive graft with improved biological characteristics, whereas S-PRF membranes were applied as an external fibrin scaffold for graft stabilization, dorsal camouflage, tip refinement, and reinforcement of the soft-tissue envelope.

Among the treated population, 1,320 patients (84.2%) underwent primary rhinoplasty, whereas 248 patients (15.8%) required revision surgery. Septal cartilage represented the principal graft source in approximately 85% of procedures, while autologous costal cartilage was harvested in the remaining 15% of cases requiring larger reconstructive support. Clinical evaluation demonstrated excellent or good aesthetic outcomes in 89% of patients, while stable graft positioning and a smooth dorsal contour were maintained in 98% of patients throughout the 12-month follow-up period. Importantly, no clinically significant cartilage

resorption was observed during follow-up. These favorable outcomes suggest that PRF may improve biological interaction between cartilage grafts and recipient tissues, thereby facilitating graft incorporation, enhancing contour stability, and reducing the likelihood of postoperative irregularities. Similar observations have recently been reported in systematic reviews evaluating PRF-assisted rhinoplasty, where the addition of platelet-rich fibrin was associated with improved graft stability, enhanced contour camouflage, and a low incidence of complications^{29,31}.

From a biological perspective, PRF should not be regarded merely as an adhesive material or space-filling substance. Instead, it functions as a transient three-dimensional fibrin scaffold containing viable platelets, leukocytes, circulating stem-cell-associated populations, cytokines, chemokines, and multiple growth factors capable of orchestrating tissue repair. During physiological degradation of the fibrin matrix, these bioactive molecules are gradually released into the surrounding tissues, supporting cellular migration, angiogenesis, extracellular matrix synthesis, and coordinated wound remodeling^{23,27}. Consequently, the contribution of PRF extends beyond simple mechanical stabilization of cartilage grafts, potentially influencing the overall quality, predictability, and biological maturation of postoperative healing.

The increasing clinical application of platelet concentrates reflects the broader evolution of regenerative medicine during the past several decades. Initial investigations into fibrin-based biomaterials demonstrated that autologous fibrin matrices could serve as effective biological substrates for tissue repair and wound healing, establishing the conceptual basis for subsequent blood-derived regenerative products¹. Further advances in centrifugation technology enabled selective concentration of platelets and biologically active proteins from peripheral blood, leading to the development of platelet-rich plasma (PRP) as one of the earliest clinically applicable platelet concentrates²³. Nevertheless, because PRP preparation requires anticoagulants and exogenous activation, concerns emerged regarding alteration of physiological coagulation and the resulting fibrin architecture. Since natural fibrin polymerization is an essential component of normal wound healing, these limitations stimulated the development of second-generation platelet concentrates capable of preserving a more physiological regenerative environment²³.

Platelet-rich fibrin represents this second generation of autologous platelet concentrates and differs fundamentally from PRP in both its preparation

protocol and biological behavior. PRF is produced without anticoagulants or artificial biochemical activation, allowing spontaneous fibrin polymerization immediately after blood collection. The resulting fibrin network entraps platelets, leukocytes, and numerous growth-factor-producing cells within a dense three-dimensional matrix that functions simultaneously as a biological scaffold and a reservoir for sustained release of regenerative mediators^{23,27,30}. These characteristics appear particularly relevant in rhinoplasty because successful cartilage grafting depends not only on the intrinsic viability of implanted cartilage but also on the quality of the surrounding soft tissues, local vascularization, and the biological processes responsible for graft incorporation. Therefore, the incorporation of I-PRF and S-PRF into cartilage grafting protocols represents a logical extension of regenerative surgical principles aimed at improving tissue adaptation while preserving structural integrity. The proposed biological mechanisms responsible for the clinical effects of PRF-assisted rhinoplasty are illustrated in Figure 10.

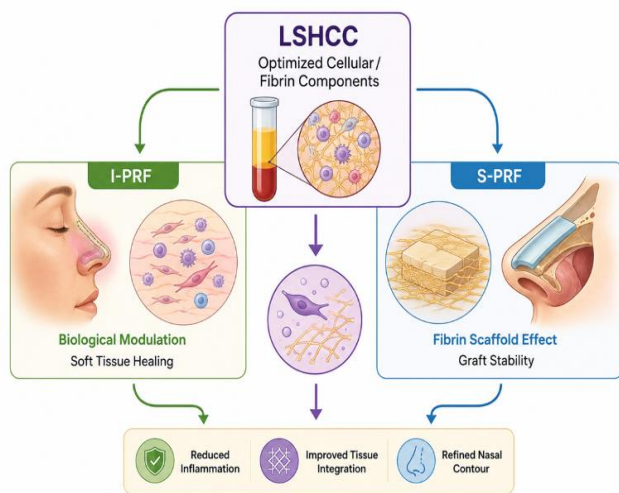


Figure 10. Proposed mechanisms of I-PRF and S-PRF application in rhinoplasty using low-speed horizontal centrifugation concept (LSHCC).

Rather than replacing conventional structural grafting techniques, I-PRF and S-PRF appear to function as complementary biological adjuncts that optimize the healing microenvironment surrounding cartilage grafts. Injectable PRF primarily contributes to biological modulation by improving graft cohesion, supporting early tissue repair, and facilitating interaction between diced cartilage particles and recipient tissues. In contrast, the solid PRF membrane provides a temporary fibrin scaffold that enhances graft stabilization, supports soft-tissue adaptation, and promotes progressive tissue remodeling. Within the framework of

the low-speed horizontal centrifugation concept (LSHCC), preservation of cellular integrity, homogeneous cellular distribution, and physiological fibrin architecture may further enhance these regenerative processes, thereby contributing to more predictable long-term structural and aesthetic outcomes.

I-PRF provides biological modulation and supports soft-tissue healing, while S-PRF acts as a fibrin scaffold promoting graft stabilization and tissue adaptation. LSHCC aims to preserve cellular distribution and fibrin architecture.

Although autologous cartilage continues to be regarded as the gold standard for nasal framework reconstruction because of its excellent biocompatibility, long-term stability, and minimal risk of immunologic reaction, several technical and biological challenges continue to influence surgical outcomes. These challenges are particularly evident in patients with thin soft-tissue envelopes, complex dorsal deformities, or those undergoing revision rhinoplasty, where even minimal contour irregularities may become clinically apparent. Furthermore, secondary rhinoplasty is frequently complicated by fibrosis, scar formation, impaired vascularity, and reduced tissue elasticity, all of which may compromise graft adaptation and limit the predictability of postoperative healing^{8,11,16}.

The introduction of diced cartilage grafting represented an important advance in dorsal augmentation and camouflage techniques. Compared with crushed cartilage, diced cartilage better preserves native chondrocyte viability and maintains the intrinsic architecture of the extracellular matrix, allowing greater conformity to irregular recipient surfaces while producing smoother dorsal contours^{12–15}.

Nevertheless, the use of multiple small cartilage fragments introduces another technical challenge, namely achieving adequate stabilization of the graft after implantation. Conventional techniques, including fascia-wrapped diced cartilage or perichondrial envelopes, have demonstrated favorable clinical outcomes but require harvesting of additional autologous tissue, thereby increasing operative time, donor-site morbidity, and overall surgical complexity^{15,22}.

Within this context, combining PRF with diced cartilage represents an evolution toward biologically enhanced rhinoplasty rather than simply a modification of conventional grafting techniques. In the protocol used in the present study, injectable PRF surrounded

individual cartilage particles with a biologically active fibrin matrix, producing a cohesive graft that was easier to manipulate and position accurately. Simultaneously, the solid PRF membrane functioned as an external biological cover that stabilized the reconstructed dorsum, protected the graft during the early postoperative period, and promoted adaptation of the overlying soft tissues. Consequently, this strategy addressed both the mechanical requirements of cartilage reconstruction and the biological conditions necessary for successful graft incorporation.

Experimental investigations provide additional support for this concept. Abd El Raouf and colleagues demonstrated that injectable PRF prepared according to the low-speed centrifugation concept significantly enhanced cartilage regeneration compared with platelet-rich plasma, showing greater preservation of cartilage morphology, increased extracellular matrix production, and improved regenerative activity²⁴. Likewise, Gode et al. reported improved viability of diced cartilage following combination with injectable PRF, suggesting that the fibrin matrix provides a favorable biological environment capable of supporting chondrocyte survival during the early stages of healing³². These experimental findings offer a biological explanation for the favorable clinical outcomes observed in the present study and reinforce the rationale for combining I-PRF with autologous diced cartilage.

An essential determinant of PRF quality is the preparation protocol itself. Accumulating evidence indicates that variations in centrifugation speed, centrifugal force, tube characteristics, processing time, and centrifuge design substantially influence the cellular composition, fibrin architecture, and biological activity of the final product^{23,27,28,30}.

The low-speed centrifugation concept proposed by Choukroun and further investigated Miron demonstrated that reducing relative centrifugal force enables greater retention of platelets and leukocytes within the fibrin matrix while preserving their biological activity^{28,30}. This concept has become increasingly important in regenerative medicine because it emphasizes preservation of cellular function rather than simply maximizing cell concentration.

Horizontal centrifugation represents a further refinement of this principle. Unlike conventional fixed-angle centrifugation, horizontal rotor systems reduce mechanical distortion during blood separation and promote a more homogeneous distribution of cellular components throughout the developing fibrin matrix²⁸. Comparative laboratory investigations have

demonstrated that horizontal centrifugation may improve preservation of regenerative cells and optimize fibrin organization, potentially enhancing the sustained release of biologically active growth factors during tissue healing^{28,30}. These observations provided the rationale for selecting the low-speed horizontal centrifugation concept (LSHCC) in the present investigation.

The dual application of injectable and solid PRF was specifically designed to exploit the complementary biological characteristics of each formulation. Injectable PRF remained in a liquid phase for several minutes following centrifugation, allowing intimate incorporation with diced cartilage before gradual fibrin polymerization occurred in situ. This produced a cohesive graft complex that facilitated handling, improved graft positioning, and reduced dispersion of cartilage fragments during implantation. In contrast, the solid PRF membrane provided immediate mechanical support while simultaneously functioning as a temporary biological scaffold capable of supporting cellular migration, neovascularization, and progressive tissue remodeling throughout the healing process^{23,27}.

One of the most practical observations arising from our clinical experience was the ability to replace conventional fascia or perichondrial wrapping techniques with S-PRF membranes. In every patient included in this series, PRF membranes provided sufficient graft coverage without the need for harvesting additional autologous tissue. Eliminating secondary donor-site procedures not only reduced operative complexity but also avoided donor-site morbidity, shortened surgical time, and simplified the reconstructive procedure. These practical advantages may be particularly valuable in revision rhinoplasty, where suitable donor tissue is often limited.

Another clinically meaningful finding involved patients presenting with intraoperative septal mucosal defects. In 110 cases, application of S-PRF membranes resulted in complete healing without postoperative septal perforation. Although this observation was not evaluated in a controlled comparative manner, it is biologically plausible considering the established regenerative properties of PRF. The fibrin scaffold may facilitate rapid cellular migration, promote early angiogenesis, support epithelial regeneration, and accelerate physiological tissue remodeling, thereby creating favorable conditions for uncomplicated mucosal healing^{23,25}.

The overall safety profile observed throughout this large prospective series was highly favorable. No

postoperative infections, hematomas, skin necrosis, allergic reactions, foreign-body responses, or graft extrusion were encountered. Minor contour irregularities requiring secondary correction occurred in only 31 patients (2%), whereas clinically significant graft displacement was documented in only two patients (0.15%). Importantly, none of the revision procedures performed during follow-up were attributable to adverse effects directly related to PRF application. These findings are consistent with recent systematic reviews and meta-analyses reporting that PRF-assisted rhinoplasty is associated with low complication rates while maintaining excellent graft stability and favorable aesthetic outcomes^{29,31,34}.

Modern rhinoplasty increasingly recognizes that successful outcomes depend not only on precise skeletal reconstruction but also on the biological quality of the overlying soft tissues. The postoperative appearance of the nose is influenced by collagen organization, vascular remodeling, tissue elasticity, and scar maturation, all of which contribute to contour definition and long-term aesthetic stability. PRF may positively influence these biological processes through the sustained release of platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and numerous additional cytokines that regulate angiogenesis, extracellular matrix synthesis, and connective tissue remodeling^{23,27}. Consequently, PRF may improve not only graft incorporation but also the quality of the soft-tissue envelope surrounding the reconstructed nasal framework.

Our clinical findings are in agreement with previous investigations evaluating the biological behavior of diced cartilage grafts. Völklein and Riechelmann demonstrated that diced cartilage preserves viable chondrocytes following implantation while progressively developing connective tissue integration within recipient sites¹².

Similarly, Dong and colleagues emphasized that predictable long-term outcomes depend largely on adequate graft stabilization and successful biological integration with surrounding tissues^{5,13}. The present findings suggest that PRF may strengthen this critical interface by providing a regenerative fibrin matrix that supports both mechanical cohesion and biological incorporation.

Recent clinical reports have further demonstrated the feasibility of PRF-assisted camouflage techniques. Beaudoin and Carles described a reproducible method

combining diced cartilage with PRF to achieve highly precise dorsal contour correction and millimetric camouflage of aesthetic irregularities, particularly in patients with thin soft-tissue coverage³³. Our experience closely parallels these observations and indicates that the combination of I-PRF, S-PRF, and diced cartilage represents a practical and biologically sound technique capable of producing smooth dorsal contours while minimizing graft visibility and postoperative irregularities.

Patient-reported outcome measures provided additional evidence supporting the clinical value of this regenerative approach. The mean postoperative satisfaction score reached 9.0 ± 0.62 on a 10-point scale, and 98% of patients reported being satisfied or highly satisfied with their surgical outcomes throughout follow-up. Although subjective assessments cannot substitute for objective clinical evaluation, patient satisfaction remains one of the most important indicators of success in aesthetic surgery because it reflects the combined influence of structural stability, functional improvement, tissue quality, and overall cosmetic appearance.

Limitations, Future Perspectives, and Practical Recommendations

Despite the encouraging findings of this prospective clinical study, several limitations should be acknowledged. Although this series represents a large clinical experience with PRF-assisted rhinoplasty, the absence of a randomized control group prevents direct comparison with conventional cartilage grafting techniques. Therefore, the present results should be interpreted as evidence supporting the safety, feasibility, and potential clinical value of this regenerative approach rather than definitive proof of its superiority.

The follow-up period was limited to 12 months, allowing assessment of early graft stability and tissue healing but not long-term cartilage remodeling or durability. Longer observational studies are needed to determine whether the biological advantages of PRF are maintained over extended follow-up.

Another limitation is the lack of standardization among currently available PRF preparation protocols. Differences in centrifugation speed, relative centrifugal force, rotor design, and processing methods may influence the cellular composition and biological activity of PRF. Although the low-speed horizontal centrifugation concept (LSHCC) was selected to

maximize preservation of regenerative components, standardized preparation protocols specifically designed for rhinoplasty remain necessary.

The biological interaction between PRF, cartilage grafts, and surrounding soft tissues also requires further investigation. Experimental evidence suggests that PRF promotes angiogenesis, cellular migration, extracellular matrix formation, and tissue remodeling; however, additional histological and molecular studies are required to clarify its precise effects on graft integration and long-term tissue regeneration. Future research should include randomized controlled trials comparing PRF-assisted rhinoplasty with conventional cartilage grafting techniques. The incorporation of objective assessment methods, including three-dimensional imaging, quantitative soft-tissue evaluation, and long-term clinical follow-up, would allow a more accurate determination of the contribution of PRF to surgical outcomes. Another promising direction is the combination of PRF with other regenerative strategies. As a natural autologous fibrin scaffold, PRF may enhance the integration of autologous tissues such as diced cartilage or fat grafts, potentially expanding individualized regenerative approaches in rhinoplasty. The role of PRF appears particularly promising in revision rhinoplasty, where fibrosis, reduced vascularity, and compromised soft tissues often limit successful reconstruction. Improving the biological environment of the recipient site may facilitate graft incorporation and improve postoperative tissue adaptation. Based on our experience, PRF should be considered a biological adjunct rather than a substitute for structural rhinoplasty. Careful surgical planning, precise cartilage grafting, and stable fixation remain fundamental for successful reconstruction. Within this framework, I-PRF may improve graft cohesion and tissue adaptation, whereas S-PRF membranes provide additional biological support, particularly in thin-skinned patients, dorsal camouflage, supratip refinement, and revision procedures. Further optimization and international standardization of PRF preparation protocols will be essential to improve reproducibility and facilitate broader clinical application of PRF-assisted rhinoplasty.

5.CONCLUSION

The results of this prospective clinical study suggest that the combination of injectable platelet-rich fibrin (I-PRF), solid platelet-rich fibrin (S-PRF) membranes, and diced autologous cartilage is a safe and effective biological adjunct in rhinoplasty. By combining structural cartilage grafting with the regenerative properties of autologous fibrin matrices, this approach

may improve graft stabilization, contour refinement, and soft-tissue adaptation while maintaining a low complication rate.

In our clinical series, PRF-assisted rhinoplasty demonstrated stable graft positioning, favorable aesthetic outcomes, and high patient satisfaction. The use of S-PRF membranes also eliminated the need for additional donor tissues, simplifying reconstruction in selected cases. Although further randomized studies with longer follow-up are required, the present findings support the use of LSHCC-prepared PRF as a valuable regenerative adjunct that complements the principles of structural rhinoplasty, particularly in dorsal camouflage, contour refinement, and revision procedures.

DECLARATIONS

Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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Ethical Approval

The study protocol was reviewed and approved by the Local Ethics Committee and was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and its subsequent amendments.

Informed Consent for Publication

All patients received both verbal and written information regarding the study and provided written informed consent for participation and publication of anonymized clinical data and photographs where applicable.

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REVIEW ARTICLE

MANAGEMENT OF LARGE IATROGENIC NASOANTRAL FISTULAS: A NARRATIVE REVIEW, EVIDENCE SYNTHESIS, AND ILLUSTRATIVE CLINICAL CASEKaren Akopian¹, Narek Harutyunyan¹, Mariam Tsaturyan¹, Tatevik Khachikyan², Levon Galstyan¹¹Maxillofacial Surgeon, Wigmore Clinic, Yerevan, Armenia²ENT, Wigmore Clinic, Yerevan, Armenia**Corresponding author:** Karen Akopian, PhD, Maxillofacial Surgeon, Wigmore Clinic, Yerevan, Armenia**e-mail** akopiankarena@gmail.com**Abstract**

Background: Large iatrogenic nasoantral fistulas remain a challenging problem in maxillofacial surgery because chronic inflammation, epithelialization of the tract, and poor local tissue quality often compromise healing. Successful treatment requires not only closure of the communication but also restoration of normal sinonasal function and long-term tissue stability.

Objective: To review contemporary surgical approaches for the management of large nasoantral fistulas and to illustrate the clinical application of current reconstructive principles through a representative clinical case.

Methods: A narrative review of the literature was performed using PubMed, Scopus, and Web of Science databases. Publications addressing nasoantral and oroantral fistulas, buccal fat pad reconstruction, palatal mucosal grafting, endoscopic sinus surgery, and postoperative stabilization techniques were analyzed. To demonstrate the practical implementation of these concepts, a patient with a large chronic iatrogenic nasoantral fistula following previous Caldwell–Luc surgery was treated using a multilayer reconstructive approach.

Results: The reviewed literature indicates that while conventional flap techniques remain effective for small defects, larger fistulas generally require more complex reconstructive strategies. Multilayer closure combining vascularized tissue support and epithelial surface coverage appears to provide greater stability and lower recurrence rates. In the presented case, reconstruction using a vascularized buccal fat pad, palatal mucosal graft, endoscopic assistance, and silicone stabilization resulted in complete closure of the fistula without postoperative complications or recurrence during follow-up.

Conclusions: Current evidence supports a biologically oriented approach for the treatment of large nasoantral fistulas. Reconstruction based on vascularized tissue transfer, epithelial barrier restoration, preservation of sinus physiology, and adequate postoperative stabilization offers a predictable solution for complex defects. The presented case illustrates the successful clinical application of these principles and highlights the importance of combining reconstructive and functional surgical concepts.

Received: May 11. 2026; **Accepted:** Jun 17. 2026; **Published:** Jul 1. 2026**Keywords:** Nasoantral fistula; Oroantral fistula; Buccal fat pad; Palatal mucosal graft; Caldwell–Luc surgery; Multilayer reconstruction; Endoscopic sinus surgery.**INTRODUCTION**

Nasoantral and oroantral fistulas are pathological communications between the maxillary sinus and the nasal or oral cavity and continue to represent a significant reconstructive challenge in maxillofacial surgery and rhinology. While small defects may occasionally close spontaneously, larger

communications often become epithelialized and progress to chronic fistulas associated with recurrent infection, persistent mucosal inflammation, impaired sinonasal function, and a substantial reduction in quality of life ^{1,2}. Successful treatment requires re-establishing the separation between the oral cavity and the maxillary sinus while preserving normal sinus function and minimizing the risk of recurrence.

The maxillary sinus is lined by specialized respiratory mucosa that maintains sinus health through an efficient mucociliary clearance system. Under physiological conditions, coordinated ciliary activity transports mucus toward the natural maxillary ostium in the middle meatus, allowing adequate drainage and ventilation^{3,4}. Disturbance of this mechanism may lead to maxillary sinus mucus retention, bacterial colonization, chronic inflammation, and progressive mucosal alterations⁵. Consequently, persistent communication between the maxillary sinus and adjacent anatomical spaces may disrupt normal sinus physiology and initiate a cycle of inflammation, impaired drainage, and tissue deterioration⁶.

For many decades, the Caldwell–Luc procedure was considered the standard surgical approach for the treatment of chronic maxillary sinus disease, odontogenic sinusitis, benign maxillary lesions, and various inflammatory conditions^{7,8}. The technique provided wide transantral access to the maxillary sinus and enabled direct removal of pathological tissue. However, its relatively radical nature frequently resulted in disruption of normal sinus mucosa and the creation of non-physiological drainage pathways. Long-term clinical and radiological studies have shown that previous Caldwell–Luc surgery can result in persistent anatomical and functional changes, including mucosal fibrosis, remodeling of the sinus walls, reduction of sinus volume, chronic mucosal thickening, and impaired ventilation^{9,10}. Such alterations may promote chronic sinonasal inflammation and create unfavorable conditions for subsequent reconstructive procedures.

A better understanding of sinonasal physiology has gradually shifted surgical management from radical procedures toward function-preserving approaches. Functional Endoscopic Sinus Surgery (FESS) focuses on maintaining mucosal integrity, restoring natural ostial drainage, and preserving mucociliary transport^{10,11}. Comparative studies have demonstrated that endoscopic techniques are associated with improved symptom control, reduced postoperative morbidity, and better preservation of long-term sinus function when compared with traditional Caldwell–Luc surgery¹¹⁻¹³. As a result, contemporary reconstruction of maxillary sinus defects increasingly aims not only to close the pathological communication but also to restore normal sinonasal physiology.

Large iatrogenic nasoantral fistulas are among the most difficult defects to manage in clinical practice¹⁴. They

may occur following Caldwell–Luc surgery, trauma, tumor resection, failed reconstructive procedures, odontogenic interventions, implant-related complications, or sinus augmentation surgery¹⁵. Defects large iatrogenic nasoantral fistulas exceeding 10 mm rarely heal spontaneously because epithelialization of the fistulous tract prevents normal tissue adhesion and closure. In addition, chronic inflammation, fibrosis, and scar formation frequently compromise local vascularity and reduce the predictability of conventional closure techniques.

From a biomechanical standpoint, reconstruction of large nasoantral fistulas presents additional challenges. Respiratory movements, coughing, sneezing, swallowing, and speech generate repetitive pressure changes across the defect site. These forces may interfere with tissue integration, impair neovascularization, and increase the likelihood of wound dehiscence or recurrence. Therefore, successful closure iatrogenic nasoantral fistulas depends not only on adequate tissue coverage but also on biological support and stable fixation during the early stages of healing¹⁶.

Numerous surgical techniques have been described for the management of nasoantral and oroantral fistulas, including buccal advancement flaps, palatal rotational flaps, buccal fat pad reconstruction, free mucosal grafts, and various multilayer closure methods¹⁷⁻²¹. Buccal advancement flaps remain widely used because of their technical simplicity, accessibility, and reliable blood supply. Nevertheless, their effectiveness decreases in larger defects due to increased flap tension, reduced tissue mobility, vestibular shortening, and a higher risk of postoperative dehiscence^{22,23}. Palatal rotational flaps provide durable keratinized tissue coverage but may be limited by donor-site morbidity and restricted mobility in extensive posterior defects.

Growing understanding of tissue biology has significantly changed the way large fistulas are reconstructed. Current evidence increasingly favors multilayer closure techniques that combine mechanical separation of anatomical compartments with enhanced vascularization and tissue regeneration^{24,25}. Among the available reconstructive options, the buccal fat pad has gained particular importance because of its close anatomical proximity, rich vascular supply, low donor-site morbidity, and capacity to support rapid tissue integration. Anatomical studies have demonstrated that the buccal fat pad receives blood supply from branches

of the facial, maxillary, and superficial temporal arteries, creating favorable conditions for graft survival and epithelialization²⁶⁻²⁹.

Beyond its vascular advantages, the buccal fat pad contains adipose-derived stromal cells and biological mediators involved in tissue repair and angiogenesis. Experimental studies have shown that VEGF and other angiogenic mediators contribute to neovascularization, further supporting the use of vascularized adipose tissue in complex reconstruction³⁰. Clinical investigations have reported favorable outcomes with buccal fat pad-based techniques in the treatment of large oroantral and nasoantral communications, including recurrent cases³¹. Although vascularized tissue provides excellent biological support, long-term success often requires restoration of a durable epithelial barrier. Palatal mucosal grafts offer keratinized epithelial coverage capable of protecting the reconstructed area from oral contamination and mechanical stress. Consequently, the combination of vascularized tissue support and epithelial surface restoration represents an important advancement in the management of large fistulas, providing both biological integration and mechanical protection³²⁻³⁴.

Postoperative stabilization is another critical factor influencing reconstructive success. Survival of free grafts depends on close adaptation between the graft and recipient bed during plasmatic imbibition, inosculation, and early vascularization. Even minimal micromovement may disrupt capillary ingrowth and compromise healing. For this reason, silicone splints have increasingly been used as supportive devices capable of stabilizing reconstructed tissues, preventing synechiae formation, and creating favorable conditions for postoperative healing³⁵⁻³⁸.

In addition to reviewing the available literature, this article presents a clinical case of a large chronic iatrogenic nasoantral fistula measuring approximately 18 × 14 mm that developed following previous Caldwell–Luc surgery. By integrating published evidence with clinical experience, we aim to discuss current reconstructive strategies for large nasoantral fistulas, examine the biological basis of multilayer soft-tissue reconstruction, and evaluate the contribution of endoscopic visualization and silicone stabilization to achieving predictable long-term functional outcomes.

MATERIALS AND METHODS

Study Design

This study was designed as a narrative review combined with an illustrative clinical case report. The primary objective was to evaluate contemporary evidence regarding the surgical management of complex nasoantral perforations and fistulas and to analyze the clinical outcomes of a reconstructive technique utilizing transseptal visualization, double-layer soft-tissue closure, and modified silicone splint stabilization.

Literature Search Strategy

A comprehensive literature search was conducted using the PubMed, Scopus, and Web of Science databases. Publications published between January 2011 and March 2026 were considered eligible for screening. The search strategy was developed to identify studies addressing the diagnosis, pathophysiology, and surgical management of nasoantral and oroantral fistulas, as well as investigations evaluating reconstructive materials and postoperative stabilization techniques.

The principal search terms included: “nasoantral fistula,” “oroantral fistula,” “oroantral communication,” “Caldwell–Luc surgery,” “buccal fat pad,” “Bichat fat pad,” “free palatal graft,” “silicone splint,” “maxillary sinus reconstruction,” “endoscopic sinus surgery,” and “double-layer closure.” Various combinations of keywords and Boolean operators (AND, OR) were used to optimize retrieval of relevant studies.

The initial electronic search identified 128 potentially relevant publications. After removal of duplicate records and preliminary screening, studies were evaluated according to their titles and abstracts. 24 publications were ultimately considered directly relevant to the objectives of the review and were included in the final evidence synthesis.

Eligibility Criteria

Studies were included if they met one or more of the following criteria:

- Investigated surgical closure of nasoantral or oroantral fistulas;
- Evaluated outcomes of buccal fat pad grafts, palatal grafts, or multilayer closure techniques;
- Examined complications and long-term consequences of Caldwell–Luc surgery;

- Assessed endoscopic approaches to maxillary sinus surgery;
- Reported clinical outcomes associated with silicone splints or other stabilization methods;
- Included randomized controlled trials, clinical studies, retrospective analyses, systematic reviews, narrative reviews, or representative case reports relevant to the management of fistulous communications.

Particular emphasis was placed on higher levels of evidence, including randomized controlled trials, comparative clinical studies, and comprehensive reviews addressing surgical outcomes and postoperative healing.

Exclusion Criteria

Studies were excluded when they:

- Were performed exclusively in animal models;
- Contained insufficient methodological information;
- Did not provide clinically relevant outcome data;
- Addressed sinonasal conditions unrelated to fistula management;
- Were duplicate publications or conference abstracts without accessible full-text data.

Evidence Synthesis

Because of the heterogeneity of study designs and outcome measures, quantitative meta-analysis was not feasible. Therefore, a qualitative evidence synthesis approach was adopted. The selected literature was analyzed according to major thematic domains, including fistula etiology, maxillary sinus physiology, complications of Caldwell–Luc surgery, reconstructive techniques, biological properties of buccal fat pad grafts, multilayer closure strategies, and postoperative stabilization methods. The findings from the literature were subsequently correlated with the diagnostic findings, surgical protocol, and postoperative outcomes observed in the presented clinical case. This integrated approach enabled the comparison of contemporary scientific evidence with real-world clinical experience and facilitated the development of evidence-based recommendations for the management of large iatrogenic nasoantral fistulas.

RESULTS

The reviewed studies indicate that the outcome of nasoantral and oroantral fistula reconstruction is influenced by multiple factors, including defect size, tissue vascularity, the condition of the surrounding mucosa, stability of wound closure, and preservation of physiological sinus drainage. Reported success rates varied among different techniques and were closely related to the biological characteristics of the recipient site.

Small fistulas (<5–10 mm) were generally associated with favorable healing when treated with conventional local flap procedures such as buccal advancement flaps and palatal rotational flaps. However, several studies reported reduced effectiveness of these techniques in larger defects because of increased flap tension, limited tissue mobility, vestibular shortening, and a higher risk of wound dehiscence.

For moderate and large defects, vascularized tissue transfer was consistently associated with more predictable clinical outcomes. The pedicled buccal fat pad flap demonstrated several advantages, including rich vascularity, rapid epithelialization, and reliable coverage of three-dimensional defects. Nevertheless, some authors noted that its use may be limited in exceptionally large defects because of insufficient tissue volume.

Free palatal mucosal grafts provided a durable epithelial barrier and good resistance to mechanical and microbial irritation. Their success, however, depended largely on the vascularity of the recipient bed, making them less predictable when used as a single reconstructive layer in poorly vascularized tissues.

Several recent studies highlighted the benefits of multilayer reconstruction. Double-layer closure techniques combining vascularized tissue support with epithelial surface coverage were associated with improved mechanical stability, enhanced tissue integration, fewer postoperative complications, and lower recurrence rates when compared with single-layer approaches.

Across the reviewed studies, multilayer reconstruction was consistently associated with the most favorable outcomes in defects larger than 10 mm, particularly when chronic inflammation, epithelialized fistulous tracts, recurrent disease, or compromised soft-tissue quality were present.

Comparative outcomes of major curgical closure techniques are presented in Table 1.

Table 1. Comparative Outcomes of Major Surgical Closure Techniques

Technique	Main Indications	Advantages	Limitations
Buccal advancement flap	Small and moderate defects	Simple technique, good accessibility	Vestibular shortening, flap tension
Palatal rotational flap	Moderate anterior defects	Provides keratinized tissue, durable coverage	Donor-site morbidity, limited mobility
Buccal fat pad flap	Large defects	Excellent vascularity, rapid healing	Limited volume in extensive defects
Free palatal mucosal graft	Surface epithelial reconstruction	Strong epithelial barrier	Requires vascularized recipient bed
PRF-assisted closure	Small defects, enhanced healing	Improved tissue regeneration, autologous material	Limited evidence for large fistulas
Double-layer closure	Large defects (>10 mm)	High stability, vascular support, predictable healing	Technically demanding
Endoscopic-assisted closure	Posterior fistulas	Improved visualization, minimally invasive access	Requires surgical experience
Transseptal endoscopic approach	Complex posterior defects	Better access and instrument control	Limited clinical availability

Biological Advantages of Double-Layer Reconstruction

A recurring finding throughout the literature was that

successful closure of large fistulas requires both reliable separation of the oral and sinus cavities and a biological environment favorable for tissue healing.

The vascularized buccal fat pad contributes to reconstruction by providing a highly perfused tissue layer capable of supporting angiogenesis and graft survival. Histological studies have shown abundant capillary networks together with regenerative properties related to adipose-derived stromal cells and angiogenic mediators.

The palatal mucosal component serves as a protective epithelial barrier that reduces bacterial contamination and mechanical irritation. The combination of a vascularized internal layer and an epithelial external layer creates favorable conditions for tissue maturation, enhances long-term stability, and reduces the risk of recurrenc. Table 2. demonstrating biological role of components used in multilayer reconstruction

Table 2. Biological Role of Components Used in Multilayer Reconstruction

Component	Biological Function	Clinical Benefit
Buccal fat pad	Vascular support and angiogenesis	Improved graft survival
Palatal mucosa	Keratinized epithelial protection	Resistance to contamination
PRF membrane	Growth factor release	Enhanced early healing
Local mucosal flap	Primary soft-tissue closure	Immediate separation of cavities

Radiological Findings and Differential Diagnosis

Several studies emphasized the importance of radiological assessment in the evaluation of complex fistulas. Cone-beam computed tomography (CBCT) allows detailed assessment of defect dimensions, sinus involvement, bone remodeling, and adjacent anatomical structures, making it a valuable tool for diagnosis and surgical planning.

Chronic postoperative fistulas were most commonly characterized by smooth bony margins, localized remodeling, and varying degrees of mucosal thickening. In contrast, aggressive pathological conditions frequently demonstrated irregular bone

destruction, invasive soft-tissue changes, and involvement of surrounding anatomical structures. Radiological findings and differential diagnosis presented in Table 3.

Table 3. Radiological Characteristics of Iatrogenic Fistulas and Aggressive Pathology

Radiological Feature	Iatrogenic Fistula	Aggressive Disease
Bone margins	Smooth remodeling and sclerosis	Irregular osteolytic destruction
Sinus mucosa	Thickening, fibrosis, fluid accumulation	Soft tissue mass formation
Adjacent structures	Preserved anatomy	Invasion and destruction
Osteomeatal complex	Inflammatory obstruction	Destructive changes

Comparison of Surgical Paradigms

The reviewed literature illustrates a gradual shift from traditional radical procedures toward more functional and minimally invasive treatment concepts. Although the Caldwell–Luc approach provides wide surgical access, extensive disruption of sinus mucosa may adversely affect long-term sinus physiology. Functional endoscopic sinus surgery (FESS) focuses on preservation of mucosal integrity, restoration of physiological drainage pathways, and maintenance of mucociliary function. Comparative studies have reported reduced postoperative morbidity, faster recovery, and improved preservation of sinus function following endoscopic management. Traditional versus functional endoscopic approaches presented in Table 3.

Table 4. Traditional Versus Functional Endoscopic Approaches

Parameter	Caldwell–Luc Approach	Functional Endoscopic Surgery
Access	Transantral radical approach	Physiological transnasal approach
Mucosal management	Extensive removal	Preservation of mucosa
Drainage	Artificial opening	Natural ostium restoration
Sinus function	Frequently	Preserved

	impaired	
Postoperative morbidity	Higher	Lower
Recovery	Longer	Faster

Postoperative Stabilization and Silicone Splints

Postoperative stabilization emerged as an important factor influencing both graft survival and long-term closure success. Several studies reported that silicone splints help maintain close adaptation between reconstructed tissues and the recipient bed, reduce graft movement, minimize hematoma formation, and decrease the likelihood of postoperative adhesions.

In addition, mechanical stabilization appears to facilitate epithelial maturation during the early stages of healing, particularly when free grafts or multilayer reconstruction techniques are used. The available literature therefore supports the use of stabilization devices as an important adjunct in the management of complex fistulous defects.

Taken together, the reviewed studies suggest that successful treatment of large nasointral and orointral fistulas depends on careful assessment of defect characteristics, tissue quality, and sinus condition. The most predictable outcomes are generally achieved when vascularized tissue support, epithelial coverage, preservation of sinus physiology, and adequate postoperative stabilization are incorporated into a comprehensive reconstructive strategy.

The findings summarized above formed the basis for the treatment approach used in the clinical case presented below. The principles of multilayer reconstruction, vascularized tissue support, preservation of sinus physiology, and postoperative stabilization were subsequently applied in the management of a large chronic iatrogenic nasointral fistula.

Clinical Application of Evidence-Based Reconstructive Principles: An Illustrative Clinical Correlation

The principles identified through the reviewed literature, including accurate defect assessment, restoration of anatomical separation, vascularized tissue support, multilayer reconstruction, and preservation of maxillary sinus function, represent essential

components for the predictable management of large chronic nasoantral communications. Their clinical relevance can be demonstrated through the following illustrative case correlation.

The presented clinical situation involved a large chronic iatrogenic nasoantral fistula characterized by persistent communication between the oral cavity and the maxillary sinus, compromised local tissue conditions, and chronic inflammatory alterations. In accordance with the reconstructive concepts emphasized in the literature, comprehensive preoperative evaluation was considered essential for defining the anatomical characteristics of the defect and selecting an appropriate closure strategy.

Cone-beam computed tomography (CBCT) assessment demonstrated a well-defined bony defect with remodeled margins and localized maxillary sinus mucosal changes, findings consistent with a chronic postoperative communication rather than an active destructive process. Preoperative imaging was used to evaluate the extent of the osseous defect, surrounding bone quality, and sinus condition for individualized reconstructive planning (Figure 1).

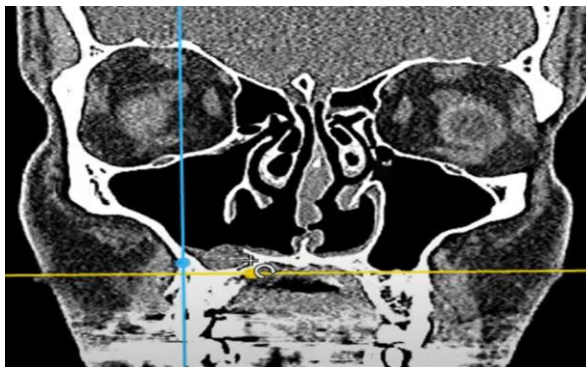


Figure 1. Preoperative radiological assessment of a chronic nasoantral communication.

Following the principles of contemporary reconstructive approaches, management was based on the concept of multilayer tissue restoration rather than simple mechanical closure. After elimination of the fistulous pathway and preparation of the recipient site, a vascularized soft tissue layer was incorporated to provide biological support and enhance tissue regeneration.

The use of a buccal fat pad flap offered a reliable vascularized component, creating a favorable environment for angiogenesis and long-term tissue

stability. Subsequent epithelial coverage with a palatal mucosal graft provided an additional protective barrier, reducing the risk of contamination and reinforcing separation between the oral cavity and maxillary sinus (Figure 2).



Figure 2. Multilayer surgical reconstruction using vascularized soft tissue and mucosal coverage.

Postoperative stabilization was performed to maintain close adaptation of the reconstructed tissues during the early healing phase. This approach reflects the evidence-based understanding that mechanical stability, protection of the repair site, and maintenance of sinus–oral separation contribute significantly to successful healing outcomes. Postoperative clinical examination together with radiological evaluation demonstrating complete epithelialization of the surgical site, stable integration of the reconstructed tissues, restoration of maxillary sinus aeration, and absence of recurrent oroantral communication during follow-up (Figure 3).



Figure 3. Postoperative fibroscopy and CT scan confirming successful epithelialization and sinus pneumatization.

This clinical correlation supports the findings of the reviewed literature, demonstrating that successful

management of large chronic nasoantral fistulas depends on a combination of anatomical reconstruction, vascularized tissue support, epithelial restoration, and appropriate control of the sinus environment. Rather than relying on a single closure technique, predictable outcomes are achieved through a biologically oriented, multilayer reconstructive strategy.

The present narrative review demonstrates that the management of large nasoantral and oroantral fistulas has progressively evolved from conventional defect closure toward a biologically oriented reconstructive concept. The analysis of current evidence indicates that successful treatment depends not only on elimination of the pathological communication but also on restoration of tissue integrity, vascular support, epithelial continuity, and preservation of maxillary sinus function^{2,18,20,34}.

The findings of this review are consistent with previous publications emphasizing that treatment selection should be based on both anatomical and biological characteristics of the defect. Earlier approaches mainly focused on mechanical closure using local flaps, including buccal advancement and palatal rotational techniques. These methods remain valuable for small and uncomplicated communications because of their simplicity, accessibility, and reliable vascularity. However, similar to observations reported in previous reviews, their predictability decreases in large chronic defects where fibrosis, epithelialized fistulous pathways, previous surgical intervention, and compromised tissue quality may reduce healing potential^{1,2,18,19,34}.

The present evidence synthesis further supports the concept that defect size alone should not determine reconstructive planning. Although limited communications may heal following single-layer closure, larger chronic fistulas require restoration of multiple tissue components. Multilayer reconstruction provides mechanical separation, vascularized support, and epithelial protection, representing a transition from simple closure toward principles of biological reconstruction^{14,16,26,27,34}.

Among available reconstructive strategies, vascularized buccal fat pad-based techniques have gained particular importance for extensive defects of the posterior maxillary region. Previous studies have demonstrated that the buccal fat pad provides favorable vascular characteristics, anatomical accessibility, minimal

donor-site morbidity, and potential regenerative properties. In comparison with non-vascularized materials, vascularized tissue transfer offers improved resistance to infection and enhances early tissue integration through continuous blood supply^{20-25,29,31}.

The reviewed literature also suggests that vascularized tissue should not be considered only as a space-filling material but as an active biological component of reconstruction. The presence of vascular and stromal elements may contribute to angiogenesis, tissue maturation, and improved wound stability. However, current evidence indicates that vascular support alone may be insufficient for long-term protection in large defects. Therefore, combined approaches incorporating an epithelial surface layer have increasingly become preferred because they simultaneously address biological integration and resistance to oral contamination^{25,30-33}.

The importance of sinus functional preservation represents another major finding of this review. Earlier surgical concepts often emphasized closure of the oral–sinus communication, whereas contemporary approaches increasingly recognize that restoration of sinus physiology is equally important. Radical procedures such as Caldwell–Luc access provide effective exposure but may alter normal sinus anatomy and mucociliary function. Modern endoscopic principles focus on maintaining physiological drainage pathways and minimizing unnecessary tissue disruption. Therefore, current management increasingly combines reconstructive closure with functional sinus rehabilitation^{7-12,41,42}.

Another important trend identified in the literature is the integration of minimally invasive visualization techniques. Endoscopic assessment and advanced imaging methods allow more accurate evaluation of fistula morphology, sinus conditions, and surrounding structures. These technologies may improve surgical precision, especially in anatomically complex defects, while reducing unnecessary tissue trauma^{6,11,13,44,46}.

The role of postoperative stabilization is also increasingly recognized. Healing after multilayer reconstruction depends on maintaining stable contact between tissues and preventing early displacement. The use of supportive measures during the initial healing period may improve adaptation of reconstructed tissues and create favorable conditions for epithelial maturation^{21,35,36-38}.

The clinical correlation presented in this review demonstrates the practical application of these evidence-based principles. The combination of vascularized buccal fat pad reconstruction, palatal epithelial coverage, and postoperative stabilization reflected the reconstructive concepts identified in the literature and resulted in stable restoration of the oral-sinus barrier. This clinical example supports the concept that predictable outcomes are achieved through integration of anatomical repair, biological support, and functional management rather than through a single surgical maneuver^{14,20,26,27,31}.

Compared with previous reviews that primarily focused on closure techniques, the current synthesis highlights a broader reconstructive philosophy emphasizing tissue quality, vascularization, sinus physiology, and long-term functional recovery. Nevertheless, available evidence remains heterogeneous, and definitive treatment algorithms are still limited^{2,20,34}.

LIMITATIONS OF CURRENT EVIDENCE

Despite significant advances in the management of nasoantral and oroantral fistulas, several limitations remain within the current literature. Most available studies are based on retrospective analyses, case series, and clinical reports, while high-quality prospective comparative studies remain limited^{1,2,19,34}.

Direct comparison between treatment modalities is difficult because published studies include heterogeneous patient populations with differences in defect size, chronicity, previous surgery, infection status, sinus pathology, and follow-up duration. In addition, standardized criteria for evaluating treatment success are not consistently applied. Many studies primarily report anatomical closure rates, whereas fewer evaluate long-term sinus function, patient-reported outcomes, and quality of life^{1,18,19,34}. The role of regenerative approaches, including platelet-rich fibrin, growth-factor-based therapies, and tissue-engineering concepts, remains promising but requires further clinical validation. Current evidence suggests potential benefits for healing enhancement; however, these approaches cannot yet replace established vascularized reconstructive techniques in large complex defects^{30,32,33}.

The present clinical correlation should also be interpreted within the limitations of an illustrative application rather than a comparative clinical trial. Its

purpose is to demonstrate the translation of evidence-based principles into clinical practice rather than to establish superiority of a specific technique^{14,16,26,27}.

FUTURE TRENDS

Future directions in nasoantral and oroantral fistula reconstruction are expected to focus on individualized, minimally invasive, and biologically enhanced treatment strategies^{11,13,16,32}.

Three-dimensional imaging, CBCT-based assessment, and digital surgical planning are becoming increasingly important for precise evaluation of defect morphology and selection of appropriate reconstructive approaches. These technologies allow better understanding of the relationship between the fistula, maxillary sinus, and surrounding anatomical structures^{3,4,6,15}.

The combination of endoscopic sinus management with multilayer oral reconstruction represents another important development. Hybrid approaches may improve management of complex posterior defects by combining accurate sinus control with reliable tissue reconstruction while preserving physiological drainage^{11,13,41,42}. Regenerative medicine may further influence future treatment through advanced biomaterials, growth-factor delivery systems, and tissue-engineered constructs designed to enhance vascularization and accelerate tissue maturation. However, their clinical role should be established through well-designed prospective studies^{25,30,32,33}. Future research should focus on multicenter clinical trials, standardized outcome measurements, and long-term assessment of functional recovery. The development of patient-specific biomaterials, digitally guided reconstruction, and individualized biological treatment protocols may represent the next stage in fistula management^{16,25,30,32}.

CONCLUSIONS

Management of large nasoantral and oroantral fistulas requires an integrated approach combining anatomical reconstruction, tissue biology, and preservation of sinus function. The evidence reviewed demonstrates that while conventional single-layer closure remains effective for limited defects, large chronic communications benefit from multilayer reconstruction strategies supported by vascularized tissue and epithelial restoration. Contemporary treatment concepts have shifted from simple closure toward biologically guided reconstruction, where vascular support,

mechanical stability, and sinus physiology are considered essential components of long-term success. The illustrative clinical application presented in this review demonstrates how these principles can be translated into practice. The combination of vascularized tissue transfer, epithelial barrier restoration, and postoperative stabilization provided predictable healing and restoration of the oral-sinus separation. Future advances will likely depend on integration of modern imaging, minimally invasive sinus management, regenerative technologies, and personalized reconstructive planning to achieve improved functional and long-term outcomes.

DECLARATIONS

Conflict of Interest

The author declare no conflict of interest.

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Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

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REVIEW ARTICLE

RETROBULBAR HEMORRHAGE: CURRENT CONCEPTS IN PATHOPHYSIOLOGY, EARLY RECOGNITION, AND EMERGENCY MANAGEMENT

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ABSTRACT

Background: Retrobulbar hemorrhage (RBH) is an uncommon yet potentially vision-threatening orbital emergency characterised by bleeding within the retrobulbar space, resulting in a rapid rise in intraorbital pressure and risk of optic nerve ischemia.

Objective: This review aims to summarise the current evidence regarding the aetiology, clinical presentation, diagnosis and management strategies of RBH, with a focus on timely intervention and improved outcomes.

Methods: A narrative review of the literature was conducted, focusing on the aetiology, pathophysiology, clinical features, and therapeutic approaches associated with RBH in trauma, surgical, and non-traumatic settings.

Results: Retrobulbar hemorrhage (RBH) most commonly follows facial trauma, orbital or maxillofacial surgery, and local anaesthetic injections, although vascular abnormalities and coagulopathies may also contribute. Clinically, it presents with proptosis, severe orbital pain, reduced visual acuity, ophthalmoplegia, and relative afferent pupillary defect. Prompt recognition is essential to prevent irreversible vision loss. Management includes medical reduction of intraocular and intraorbital pressure; however, emergency lateral canthotomy and cantholysis remain the definitive vision-saving interventions when optic nerve perfusion is compromised.

Conclusion: RBH requires immediate diagnosis and management to prevent permanent vision loss. Increased awareness, perioperative vigilance, and standardised emergency protocols are essential for enhancing clinical outcomes and minimising associated morbidity.

Keywords: Canthotomy, Cantholysis; Compartment syndrome; Retrobulbar hemorrhage (RBH).

INTRODUCTION

Retrobulbar hemorrhage (RBH) is an uncommon but potentially devastating orbital emergency that demands immediate recognition and intervention to prevent irreversible visual impairment. RBH leads to a rapid elevation of intraorbital pressure due to the rigid confines of the bony orbit. Even small increases in orbital volume can precipitate orbital compartment syndrome (OCS), compromising optic nerve perfusion and retinal circulation. If left unaddressed, ischemic

injury may occur within minutes, leading to visual impairment or permanent loss of vision¹. The aetiology of RBH is diverse. Trauma remains the most common cause, particularly in association with midfacial injuries, zygomaticomaxillary complex fractures, and orbital blowout fractures. Surgical interventions involving the orbit, eyelids, sinuses, and maxillofacial region also represent significant risk factors. Retrobulbar injections administered during ophthalmic anaesthesia, cosmetic procedures such as

blepharoplasty, and endoscopic sinus surgery have all been linked to iatrogenic RBH ². Additionally, systemic conditions, including hypertension, coagulopathies, anticoagulant therapy, and vascular malformations, can predispose patients to spontaneous hemorrhage within the orbital compartment ¹⁹. For oral and maxillofacial surgeons, the relevance of RBH is significant. Many maxillofacial trauma cases and surgical procedures place the orbital contents at risk, and failure to recognize RBH can lead to preventable blindness. Therefore, a thorough understanding of the anatomical considerations, mechanisms of injury, clinical presentation, and emergency management protocols is essential. Despite being rare, RBH carries disproportionately high morbidity relative to its incidence, and published literature continues to emphasize the importance of rapid, informed decision-making to optimize visual outcomes.

ANATOMY OF RETROBULBAR SPACE

The retrobulbar space, also referred to as the intraconal space, is the compartment located posterior to the globe and enclosed by the four rectus muscles that converge posteriorly at the annulus of Zinn. This space contains critical neurovascular and muscular structures, including the optic nerve, ophthalmic artery, ciliary nerves, ciliary ganglion, and adipose tissue that cushions and stabilizes the globe. The extraocular muscles form a conical boundary, with the optic nerve occupying the central axis as it travels posteriorly from the globe to the optic canal. Laterally, the space is bordered by the lateral rectus muscle and the lacrimal gland fossa; medially by the medial rectus muscle and ethmoid air cells; superiorly by the superior rectus–levator palpebrae superioris complex; and inferiorly by the inferior rectus muscle. The orbital walls provide rigid containment, such that even small increases in volume, such as those caused by bleeding, can rapidly elevate intraorbital pressure. This tightly confined arrangement makes the retrobulbar space particularly vulnerable to compressive pathology, especially acute hemorrhage, which can threaten optic nerve perfusion. The adipose tissue within the intraconal compartment facilitates smooth ocular movements, while the neurovascular bundles traverse the space to supply the globe and extraocular muscles. Because the orbital septum restricts anterior expansion, pathological processes within the retrobulbar space typically expand posteriorly or exert forward pressure on the globe. Understanding the anatomical layout of this space is essential for diagnosing and managing conditions such as retrobulbar hemorrhage, optic neuropathies, and surgical complications.

ETIOLOGY

Retrobulbar hemorrhage can be caused by surgical reduction of orbital and mid-face fractures, cosmetic or reconstructive eyelid operations, endoscopic sinus procedures, retrobulbar injections, blunt trauma, and

thrombolytic agents ⁴. A retrospective study on orbital fractures reveals that the incidence of RBH is approximately 1.3%. The overall incidence of retrobulbar hemorrhage in maxillofacial trauma is roughly 1–4%, depending on the nature and severity of the fractures and the study population ⁵⁻⁶. Local anaesthesia in the retrobulbar space is a traditional method for providing akinesia and analgesia to the eye during surgical procedures. However, this treatment is rarely complicated by the occurrence of RBH (incidence: 0.75%), which poses a potential risk to vision loss ⁴. RBH occurs when bleeding develops within the limited retrobulbar or intraconal space, most typically caused by disruption of the arterial or venous network in the orbit.

RBH likely occurs due to 3 major causes (**Fig. 1**)

- 1) Trauma is the most frequent etiological cause, especially blunt periorbital injuries, zygomaticomaxillary fractures, and penetrating orbital trauma, which may disrupt the ophthalmic artery, ciliary arteries, or orbital veins.
- 2) Non-traumatic causes include vascular malformations, spontaneous bleeding from hypertension, coagulopathies, anticoagulant or antiplatelet medication, and systemic disorders like hemophilia or liver dysfunction that impede haemostasis.
- 3) Iatrogenic causes include periocular surgeries such as blepharoplasty, endoscopic sinus surgery, and retrobulbar or peribulbar anaesthetic injections, when unintentional vascular perforation can result in rapid blood accumulation ^{4,7}.

Postoperative factors such as uncontrolled hypertension, coughing, Valsalva maneuvers, and anticoagulant use may precipitate delayed bleeding in vulnerable patients. Because the orbit is a non-expandable compartment, even minimal bleeding during maxillofacial procedures can rapidly elevate intraorbital pressure, underscoring the importance of meticulous surgical technique, thorough understanding of orbital anatomy, and prompt recognition of visual symptoms ³.

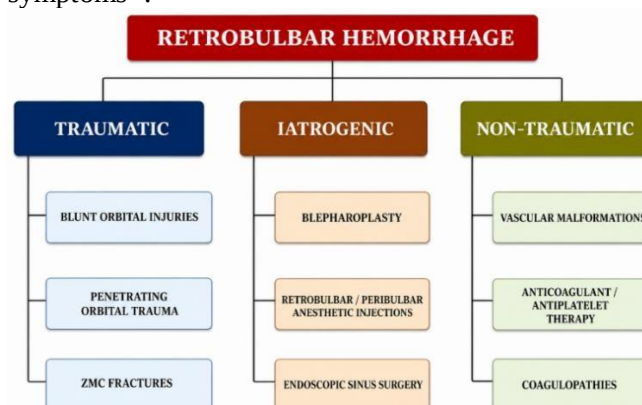


Figure 1. Etiology of Retrobulbar Hemorrhage (RBH)

PATHOPHYSIOLOGY

The orbit is a rigid, non-distensible bony cavity containing the globe, extraocular muscles, optic nerve, orbital fat, and a dense vascular network. Consequently, even a small orbital hemorrhage can significantly increase intraorbital pressure, causing anterior displacement of the globe⁷. Elevated pressure compresses the optic nerve, central retinal artery, and short posterior ciliary arteries, resulting in retinal and optic nerve ischemia. Progressive pressure further impairs venous outflow through the superior and inferior ophthalmic veins, leading to venous congestion, worsening proptosis, and expansion of hematoma⁶. The orbital septum restricts anterior decompression, directing hemorrhagic expansion posteriorly toward the optic nerve. When intraorbital pressure exceeds central retinal artery pressure, retinal perfusion ceases, potentially causing irreversible vision loss (**Fig. 2**). Concurrent compression of the extraocular muscles and stretching of the optic nerve contribute to ophthalmoplegia and impaired axonal transport.

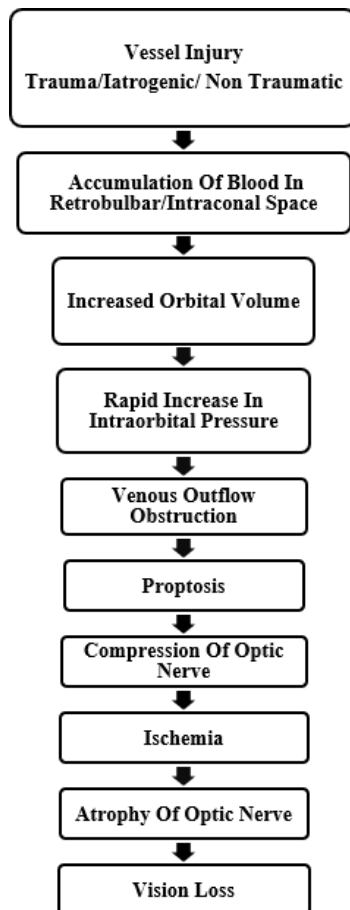


Figure 2 Pathophysiological sequence of Retrobulbar hemorrhage (RBH)

CLINICAL FEATURES

All patients presenting with orbital injuries or midfacial fractures should undergo a complete ophthalmologic

examination¹⁰. The most common signs and symptoms include pain, proptosis, chemosis, diplopia, subconjunctival hemorrhage, increased intraocular pressure, a tense globe, decreased visual acuity, loss of the direct pupillary light reflex, or ophthalmoplegia^{4,7-8}. The appearance & size of the hemorrhage were graded on a four-point scale: (1-spot ecchymosis), (2-lid ecchymosis involving half of the lid surface area or less), (3-lid ecchymosis all around the eye with no increase in intraocular pressure), (4-retrobulbar hemorrhage with elevated intraocular pressure)^{4,10}. If these signs are not recognized early, the outcome could result in complete loss of vision in the affected eye. Prevention, recognition, and intervention are therefore crucial to prevent those devastating conditions⁷.

MANAGEMENT:

The management of retrobulbar hemorrhage (RBH) is a time-critical emergency aimed at rapidly decompressing the orbit, preserving optic nerve perfusion, and preventing irreversible visual loss. Under physiological conditions, normal intraorbital pressure ranges from 3 to 6 mmHg¹¹. It can rise to many times the normal value in the event of RBH, producing a vision-threatening compartment syndrome. In animal studies, it has been shown that ischaemia, due to transient central retinal artery occlusion, is well tolerated up to 100 min; however, irreparable damage can occur after ischaemia of 105 min¹². After a diagnosis of retrobulbar hemorrhage, Prompt orbital decompression is essential to preserve optic nerve function. It has been stated that if decompression is carried out within 2 hours of the onset of symptoms, it is likely to be successful in avoiding permanent damage. According to Erickson et al., emergent orbital decompression is indicated when relative proptosis, significant eyelid tightness resistant to digital opening, and a relative afferent pupillary defect are present concurrently. Collectively, these findings strongly indicate optic nerve ischemia secondary to orbital compartment syndrome and warrant immediate surgical management to prevent permanent visual loss.⁸. If proptosis or tight lids are present after orbital trauma, clinicians should promptly check for RAPD rather than other vital signs, such as visual acuity, IOP, or extraocular movements, which can lead to unnecessary delay in vision-saving procedures. Patients presenting with proptosis, marked eyelid tension in the absence of voluntary squeezing, or a substantial preseptal haematoma should undergo urgent orbital decompression. In contrast, the presence of a relative afferent pupillary defect (RAPD) without associated proptosis or eyelid tightness is more suggestive of optic neuropathy resulting from a pressure-independent mechanism. In such cases, lateral canthotomy and cantholysis are unlikely to provide therapeutic benefit. Regular eye examinations are required after surgical reduction of zygomatic/orbital fractures to assess the

RBH in early stages. Hayter and Sugar created an orbital observation chart, which is currently widely used in many centers to record observations of orbital pain, visual acuity, proptosis, direct light reflex, and pupil size¹³. Once the clinical diagnosis of retrobulbar hemorrhage is made, treatment should begin immediately and involves both medical and surgical procedures. Additional investigations, such as CT or ultrasound scans, should not delay treatment once a clinical diagnosis has been established. Management of RBH encompasses both medical and surgical methods, as reported in the literature, and is outlined in (Fig. 3).

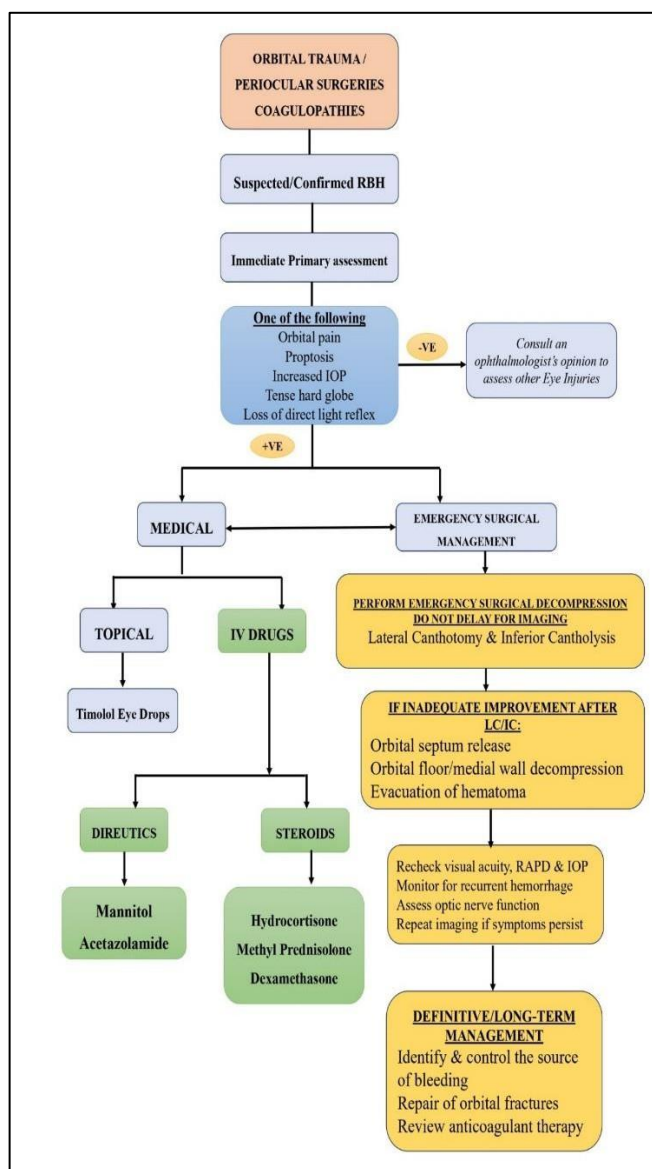


Figure 3. Clinical management algorithm for the diagnosis and emergency treatment of Retrobulbar hemorrhage. (RBH)

Medical management may be used as an adjunct to surgical decompression or in selected mild cases. It includes Diuretics (mannitol, acetazolamide), corticosteroids (Methylprednisolone, Dexamethasone, or Hydrocortisone,) and topical beta blockers like Timolol eye drops are used.

Intravenous administration of Acetazolamide 500 mg or hydrocortisone 100 mg can be given. A rapid infusion of 20% mannitol can also be used¹⁴. If vision does not improve within 30 to 45 minutes, surgical intervention is necessary.

Carbonic Anhydrase inhibitors, such as acetazolamide, lower intraocular pressure by inhibiting carbonic anhydrase, which significantly reduces aqueous humor output. Hyperosmotic agents, such as mannitol, shrink the vitreous and reduce the volume of tissue in the orbit⁴. Corticosteroids such as dexamethasone can reduce inflammation and stabilize cell membranes against ischemic damage. Wood et al. reported a case in which intravenous mannitol, acetazolamide, and hydrocortisone were administered for the management of retrobulbar hemorrhage, resulting in significant improvement in visual acuity within six hours without the need for surgical decompression⁷.

Conservative treatment should be continued for five to seven days if there is a decrease in local signs & symptoms and an improvement in vision¹⁵.

Other nonsurgical therapeutic approaches are recommended, including the use of timolol maleate eye drops, 0.25% topical solution, 1 to 2 drops daily, which functions by decreasing the production of aqueous humor. Additional conservative strategies that may be overlooked include elevating the head, applying topical ice packs, and avoiding dressings that can be tight and potentially elevate intraocular pressure¹⁸.

Lateral canthotomy with inferior cantholysis is the most widely accepted surgical decompression technique for retrobulbar hemorrhage. Goodall et al. demonstrated that combining pharmacological therapy with surgical decompression improves visual outcomes and reduces the risk of permanent blindness. Once acute RBH is diagnosed, immediate lateral canthotomy and inferior cantholysis should be performed, as the procedure is simple, effective, and can be carried out under local anaesthesia in an outpatient or emergency setting¹⁷.

Lateral Canthotomy & Inferior Cantholysis: The inferior and superior crus of the lateral canthal tendon attach to the inner part of the lateral orbital rim, known as Whitnall's tubercle. The lateral canthotomy involves placing an artery clip between the upper and lower lids, moving towards the orbital rim, and crushing the tissues. With the sharp dissection scissors, the lateral canthal tendon is incised, followed by inferior cantholysis.

The lateral canthal tendon is separated from the skin anteriorly and the conjunctiva posteriorly. The inferior crus of the lateral canthal tendon is entirely disinserted, allowing the lower lid to move freely to evacuate the hematoma^{4,17,19}.

PREVENTION:

Preventing retrobulbar hemorrhage requires careful planning preoperatively, intraoperatively, and postoperatively for orbital/maxillofacial procedures and

ophthalmic surgeries. Pre-operatively, identifying high-risk patients, such as those with hypertension, coagulation disorders, or on anticoagulant therapy, is essential, along with optimizing systemic conditions and reviewing orbital anatomy. Intra-operatively, prevention focuses on gentle dissection, avoiding deep or blind instrumentation, and achieving meticulous hemostasis while maintaining stable blood pressure and minimising Valsalva or coughing. Post-operatively, prevention includes avoiding tight dressings, elevating the head to reduce venous pressure, and monitoring early warning signs like pain, proptosis, or visual changes. Educating patients to prevent straining, heavy lifting, and forceful nose blowing further reduces their risk. These combined measures significantly lower the likelihood of retrobulbar hemorrhage and its vision-threatening complications (**Fig.4**)

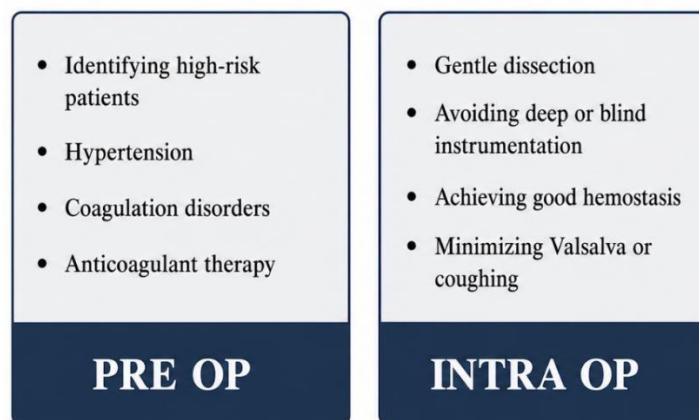


Figure4.Preoperative, intraoperative, and postoperative strategies for the prevention of Retrobulbar hemorrhage (RBH).

CONCLUSION

Retrobulbar hemorrhage (RBH) remains a rare but potentially vision-threatening complication encountered in orbital, ophthalmic, maxillofacial, and trauma-related procedures. Early recognition, rapid intervention, and adherence to well-defined preventive strategies are essential to minimize morbidity. A thorough understanding of orbital anatomy, meticulous surgical technique, and vigilant perioperative monitoring significantly reduce the risk of RBH and its complications.

DECLARATIONS

Acknowledgment

Declared none.

Conflict of Interest

The author declare no conflict of interest.

Funding

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Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

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CASE REPORT

CUSTOMIZED TITANIUM MESH RECONSTRUCTION OF A SEVERELY ATROPHIC MANDIBLE WITH SUBSEQUENT IMPLANT-SUPPORTED REHABILITATION: A CASE REPORTKaren Akopian¹, Narek Harutyunyan¹, Levon Galstyan¹¹Maxillofacial Surgeon, Wigmore Clinic, Yerevan, Armenia**Corresponding author:** Karen Akopian, PhD, Maxillofacial Surgeon, Wigmore Clinic, Yerevan, Armenia**e-mail** akopiankarena@gmail.com**Received:** Jun 15, 2026; **Accepted:** Aug 2, 2026; **Published:** Aug 9, 2026**Abstract**

Background: Severe mandibular alveolar ridge atrophy represents a major challenge in implant dentistry, especially when associated with advanced periodontal destruction and extensive loss of supporting bone. In cases where residual bone volume is insufficient for prosthetically guided implant placement, guided bone regeneration (GBR) provides an effective approach for restoring the three-dimensional architecture of the alveolar ridge.

Case Presentation: A systemically healthy female patient with Stage III generalized chronic periodontitis and severe mandibular alveolar bone loss was referred for implant-supported rehabilitation. Six non-restorable mandibular anterior teeth were extracted due to advanced periodontal destruction and poor long-term prognosis. Immediate ridge augmentation was performed following extraction and surgical debridement of the sites.

The deficient mandibular ridge was reconstructed using a graft mixture consisting of 60% deproteinized bovine bone mineral (Bio-Oss®) and 40% autogenous bone. The graft material was stabilized with a patient-specific CAD/CAM titanium mesh designed according to preoperative cone-beam computed tomography (CBCT) evaluation and virtual planning.

During the six-month healing period, the augmented ridge maintained its planned contour without wound dehiscence, infection, graft exposure, or titanium mesh exposure. CBCT evaluation demonstrated adequate bone regeneration for implant placement. After removal of the customized titanium mesh, eight BioHorizons implants were placed in prosthetically planned positions. Primary stability was achieved in all implants, with insertion torque values of approximately 35 Ncm.

Following a three-month osseointegration period, a definitive implant-supported metal-ceramic fixed bridge was fabricated and delivered. Clinical and radiographic follow-up demonstrated stable peri-implant tissues and preservation of the regenerated bone volume. During the three-year follow-up period, no implant failures, peri-implant infections, prosthetic complications, or graft-related complications were observed.

Conclusion: This case demonstrates that customized CAD/CAM titanium mesh-assisted guided bone regeneration combined with a mixture of deproteinized bovine bone mineral and autogenous bone can provide predictable reconstruction of severely atrophic mandibular ridges. The technique allowed stable three-dimensional bone regeneration, successful implant placement, and long-term functional and esthetic rehabilitation.

Keywords: Guided bone regeneration, titanium mesh, Bio-Oss, autogenous bone graft, mandibular atrophy, ridge augmentation, dental implants.

INTRODUCTION

Severe mandibular alveolar ridge atrophy remains a complex clinical challenge in implant dentistry. Following tooth extraction, alveolar bone remodeling is a physiological process; however, this resorptive pattern may become considerably more pronounced in patients with advanced periodontal disease, chronic

inflammatory conditions, trauma, or prolonged edentulism¹. As the remaining bone volume decreases, placement of dental implants in an ideal prosthetic position may become difficult or impossible without prior reconstructive treatment aimed at restoring adequate ridge height and width^{2,3}. Different surgical approaches have been described for the management of severely resorbed alveolar ridges. These include

autogenous block bone grafting, ridge splitting techniques, distraction osteogenesis, inferior alveolar nerve repositioning, and guided bone regeneration (GBR) procedures³⁻⁵. Autogenous bone remains an important grafting material due to its osteogenic, osteoinductive, and osteoconductive properties. Nevertheless, limitations such as donor-site morbidity, limited availability of harvested bone, additional surgical procedures, and possible postoperative volume reduction have led clinicians to investigate alternative or combined regenerative approaches⁶. Over the past decades, guided bone regeneration has become a widely used method for reconstruction of deficient alveolar ridges⁷. The principle of GBR is based on the use of a barrier that prevents the migration of rapidly proliferating soft tissues into the bone defect while maintaining a protected environment that supports the migration and activity of osteogenic cells⁸. The success of this approach depends on several biological and technical factors, including primary wound closure, sufficient blood supply, stable immobilization of the graft material, preservation of the regenerative space, and protection of the newly forming tissue. These concepts were summarized by Wang and Boyapati as the PASS principles⁹.

The PASS concept includes four essential requirements for predictable bone regeneration:

- Primary wound closure
- Angiogenesis and adequate blood supply
- Space creation and maintenance
- Stability of the wound and regenerative site

The selection of an appropriate graft material is an important factor influencing the outcome of GBR procedures. Deproteinized bovine bone mineral (DBBM; Bio-Oss®) is one of the most extensively studied xenogeneic biomaterials used in implant dentistry. Its porous structure, favorable osteoconductive characteristics, and slow resorption pattern allow it to function as a stable scaffold supporting new bone formation and contributing to maintenance of the augmented ridge volume over time^{10,11}. In cases involving severe mandibular atrophy, the combination of xenogeneic bone substitutes with autogenous bone may provide additional biological advantages. Autogenous bone contains viable cells and biological factors that may contribute to early bone formation, whereas Bio-Oss® provides a slowly resorbing mineral scaffold that supports long-term volume preservation. Therefore, combining autogenous bone with Bio-Oss® may create a balanced regenerative environment by integrating the biological

activity of autogenous grafts with the dimensional stability of xenogeneic materials¹²⁻¹⁴. In the present case, a graft mixture composed of 60% deproteinized bovine bone mineral and 40% autogenous bone was used for reconstruction of a severely deficient mandibular ridge. This combination was selected to provide sufficient biological stimulation while maintaining the structural stability required for extensive ridge augmentation. One of the main challenges in GBR procedures, particularly in large vertical and horizontal defects, is the maintenance of adequate regenerative space. Pressure from the overlying soft tissues may influence graft stability and result in partial collapse of the augmented region¹⁶. To overcome this limitation, titanium meshes have been introduced as rigid non-resorbable barriers capable of maintaining graft volume and preserving the intended three-dimensional shape of the reconstructed ridge during healing^{17,18}. Titanium meshes provide mechanical stability, excellent biocompatibility, and resistance to deformation. Their ability to stabilize particulate graft materials makes them especially useful in extensive alveolar defects where conventional membrane techniques may not provide sufficient space maintenance¹⁹. The introduction of digital planning and CAD/CAM manufacturing has further improved the application of titanium mesh-assisted GBR. Patient-specific titanium meshes can be designed from CBCT-based virtual planning according to the individual anatomy of the defect. This allows more accurate adaptation, decreases the need for intraoperative modification, and improves stabilization of the grafted area²⁰. Current clinical evidence supports the use of titanium mesh-assisted GBR in complex alveolar reconstruction. Systematic reviews and meta-analyses have reported favorable vertical and horizontal bone augmentation outcomes together with high implant survival rates following titanium mesh-based regeneration procedures^{21,22}. In addition, recent studies comparing CAD/CAM-designed titanium meshes with conventionally shaped meshes have demonstrated improved adaptation, reduced surgical adjustments, and enhanced clinical predictability when individualized designs are used²³. Therefore, the combination of a patient-specific titanium mesh with a graft mixture containing deproteinized bovine bone mineral and autogenous bone represents a biologically supported approach for reconstruction of severely atrophic mandibular ridges. This method provides stable space maintenance, facilitates bone regeneration, reduces the need for extensive donor-site harvesting, and creates a suitable foundation for subsequent implant placement²⁴. The aim of this case report is to describe the reconstruction of a severely atrophic mandible after

extraction of hopeless teeth using guided bone regeneration with a customized CAD/CAM titanium mesh and a graft mixture consisting of 60% Bio-Oss® and 40% autogenous bone, followed by implant placement and implant-supported prosthetic rehabilitation.

CASE REPORT

Patient Assessment

A systemically healthy female patient was referred for implant-supported rehabilitation of the mandible. Clinical examination revealed multiple mandibular teeth with a poor long-term prognosis due to severe mobility, advanced clinical attachment loss, and extensive loss of supporting alveolar bone. The patient was diagnosed with Stage III generalized chronic periodontitis associated with severe mandibular alveolar ridge destruction. The remaining mandibular anterior teeth showed advanced periodontal involvement and were considered non-restorable. The treatment plan included extraction of six mandibular anterior teeth followed by immediate guided bone regeneration (GBR) to reconstruct the deficient alveolar ridge and prepare the site for future implant placement. Cone-beam computed tomography (CBCT) was performed to evaluate the remaining bone volume and defect morphology. The radiographic examination demonstrated severe horizontal and vertical bone deficiency, with insufficient ridge dimensions for placement of implants in a prosthetically appropriate position (Figure 1a,b).

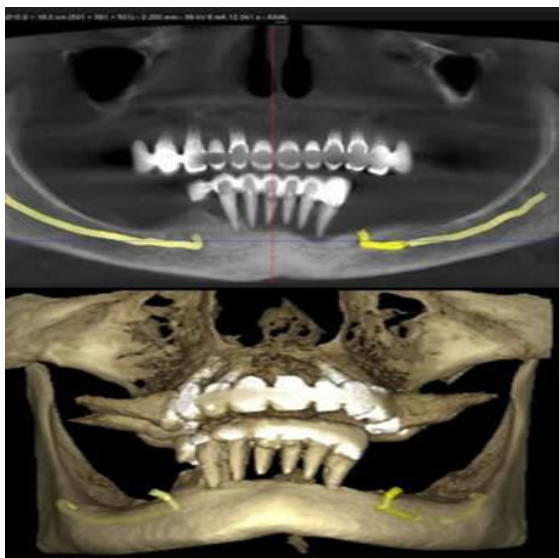


Figure 1a,b. Preoperative clinical and CBCT evaluation demonstrating severe mandibular alveolar ridge deficiency and inadequate bone volume for implant placement.

Ridge Augmentation Procedure

Following atraumatic extraction of the six compromised mandibular anterior teeth, the extraction sites were carefully debrided. The sockets were curetted and irrigated with an antiseptic solution to remove residual inflammatory tissue and prepare the recipient sites for bone regeneration. Immediate ridge augmentation was performed using a mixture of deproteinized bovine bone mineral (Bio-Oss®) and autogenous bone. The graft material was placed into the extraction sockets and adjacent deficient ridge areas to restore the lost alveolar contour. The graft mixture was adapted according to the planned implant positions to achieve three-dimensional reconstruction of the mandibular ridge (Figure 2a,b).



Figure 2a,b Application of the Bio-Oss® and autogenous bone graft mixture (60:40 ratio) for reconstruction of the deficient mandibular ridge.

After placement of the graft material, the augmented area was covered and stabilized with a customized titanium mesh. The mesh was filled with the graft mixture and positioned to maintain the required regenerative space and preserve the planned ridge dimensions during healing (Figure 3).



Figure 3. Placement of the Bio-Oss® and autogenous bone graft mixture (60:40 ratio) within the customized titanium mesh for three-dimensional augmentation of the mandibular ridge.

Placement of Customized Titanium Mesh

The patient-specific titanium mesh was designed based on preoperative CBCT data and virtual planning. The CAD/CAM-fabricated mesh was adapted to the anatomy of the mandibular defect and fixed with titanium fixation screws. The customized mesh provided stable protection of the grafted area and maintained the required space for bone regeneration during the healing period (Figure 4a,b).

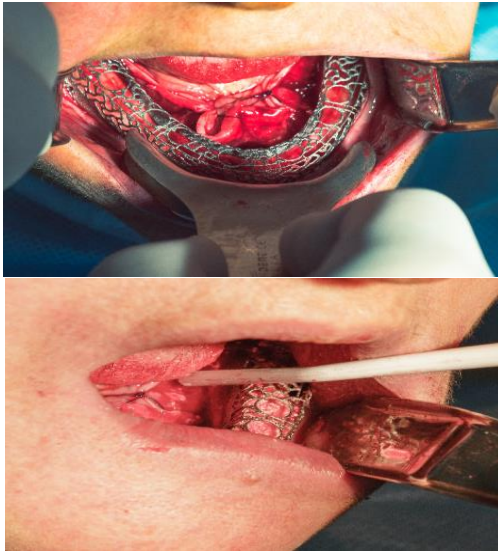


Figure 4a,b. Placement and fixation of the customized titanium mesh over the augmented mandibular ridge to maintain the planned regenerative volume.

Primary tension-free closure was achieved by flap advancement and periosteal releasing procedures. The surgical site was closed with appropriate suturing to provide stable soft tissue coverage (Figure 5).



Figure 5. Tension-free repositioning of the mucoperiosteal flap and primary closure of the surgical site after placement and fixation of the customized titanium mesh.

Healing Phase

Healing following the augmentation procedure was uneventful. Postoperative treatment included systemic

antibiotic therapy with amoxicillin/clavulanic acid for seven days, analgesic medication, and antiseptic mouth rinses with chlorhexidine during the early healing period. The patient was followed clinically and radiographically throughout the healing phase. Soft tissue healing was satisfactory, and the surgical site remained stable. No infection, wound dehiscence, graft exposure, or titanium mesh exposure was observed. After six months, CBCT evaluation demonstrated progressive mineralization of the augmented area and sufficient bone formation for implant placement. The reconstructed ridge maintained its planned shape and volume. During implant placement, the customized titanium mesh was removed. The regenerated bone appeared clinically mature, well vascularized, and suitable for implant insertion.



Figure 6. Postoperative CBCT evaluation demonstrating stable positioning of the customized titanium mesh and preservation of the augmented mandibular ridge volume during the healing period.

Implant Placement

Implant placement was performed six months after augmentation following confirmation of adequate bone regeneration by CBCT. Eight BioHorizons dental implants were placed in the regenerated mandibular ridge according to the prosthetically planned positions. (Figure 7). Primary implant stability was achieved in all implant sites, with insertion torque values reaching approximately 35 Ncm.

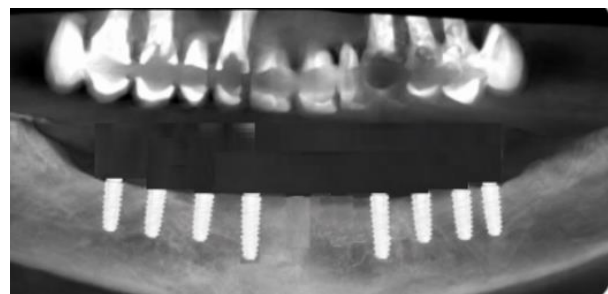


Figure 7. Postoperative CBCT, Placement of eight BioHorizons implants in the regenerated mandibular ridge demonstrating appropriate positioning and primary stability.

Prosthetic Rehabilitation

After a three-month osseointegration period, definitive implant-supported prosthetic rehabilitation was completed. The prosthetic restoration was designed to restore occlusion, masticatory function, phonetics, and esthetic appearance. Clinical and radiographic examinations after prosthetic loading demonstrated stable peri-implant tissues and satisfactory functional conditions (Figure 8).

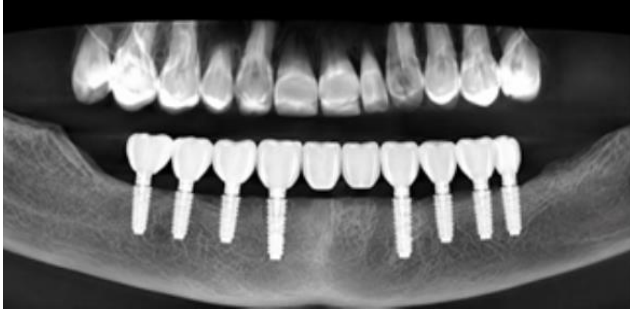


Figure 8. CBCT evaluation demonstrating A metal-ceramic fixed bridge supported by the 8 implants

During the three-year follow-up period, all implants remained clinically stable and functional. No implant loss, peri-implant infection, prosthetic fracture, screw loosening, or graft-related complications were observed. Radiographic evaluation confirmed maintained osseointegration and preservation of the regenerated bone volume. Marginal bone changes around the implants remained within physiological limits, with no evidence of progressive peri-implant bone loss. The final rehabilitation provided stable occlusion, improved masticatory efficiency, satisfactory phonetic function, and acceptable esthetic integration.

DISCUSSION

The present case demonstrates the clinical application of guided bone regeneration using a customized CAD/CAM titanium mesh combined with a mixture of deproteinized bovine bone mineral (Bio-Oss®) and autogenous bone for reconstruction of a severely atrophic mandible.

Severe mandibular ridge atrophy remains a challenging condition in implant dentistry, particularly when bone loss is associated with advanced periodontal destruction. Progressive alveolar resorption after tooth loss may result in combined horizontal and vertical defects, making implant placement in an ideal prosthetic position difficult or impossible without prior reconstruction²⁵. Several surgical approaches have been proposed for management of severe alveolar

defects, including autogenous block grafting, ridge expansion, distraction osteogenesis, and guided bone regeneration²⁶⁻³¹. Although autogenous bone remains an important graft material because of its osteogenic, osteoinductive, and osteoconductive properties³²⁻³⁴, its use may be limited by donor-site morbidity, restricted graft availability, additional surgical procedures, and increased patient discomfort^{35,36}.

For this reason, GBR has become an established technique for reconstruction of deficient alveolar ridges. The biological basis of GBR is the maintenance of a protected regenerative environment that prevents soft tissue invasion and allows bone-forming cells to repopulate the defect area.

The principles described by Wang and Boyapati in the PASS concept emphasize the importance of primary closure, angiogenesis, space maintenance, and stability for successful regeneration⁹.

In the present case, these principles were applied during the entire regenerative procedure. Following extraction of the non-restorable teeth, the deficient mandibular ridge was immediately reconstructed using a combination of Bio-Oss® and autogenous bone in a 60:40 ratio. This combination was selected to provide both biological activity and long-term volume stability.

The use of a mixed graft material may offer advantages in large defects. Autogenous bone contributes viable cells and growth factors that may support early bone formation, while deproteinized bovine bone mineral provides a slowly resorbing scaffold that helps maintain the regenerated volume over time¹²⁻¹⁴. In this case, the regenerated ridge demonstrated sufficient volume and quality to allow placement of implants in prosthetically planned positions.

A key factor in the outcome was the stabilization of the grafted area with a customized titanium mesh. Titanium meshes have been widely used in GBR because they provide mechanical support and maintain the regenerative space required for bone formation¹⁷⁻¹⁹. However, conventional meshes often require intraoperative adaptation, which may increase surgical manipulation.

The use of CAD/CAM technology allows fabrication of patient-specific titanium meshes based on CBCT data and virtual planning. This approach provides accurate adaptation to the defect anatomy and facilitates reconstruction of the desired ridge contour^{20,23}.

In this patient, the customized titanium mesh acted as a rigid framework that protected the graft material from soft tissue pressure and prevented collapse of the augmented area during healing. The stable maintenance of the regenerative space contributed to the formation of an adequate ridge for subsequent implant placement. The clinical findings are consistent with previous reports describing favorable outcomes with titanium mesh-assisted GBR. Recent systematic reviews have demonstrated that titanium mesh techniques can provide reliable vertical and horizontal bone augmentation with satisfactory implant survival rates^{21,22}. Another important aspect of this treatment protocol was the reduction of the amount of harvested autogenous bone by combining it with Bio-Oss®.

This approach allowed preservation of the biological advantages of autogenous bone while avoiding extensive donor-site procedures.

The three-year follow-up after prosthetic loading represents an important finding of this case. Many augmentation reports focus mainly on bone formation and implant placement, while long-term evaluation after functional loading is less frequently described. In the present case, the regenerated bone remained stable after prosthetic rehabilitation, with maintained peri-implant tissue health and no evidence of progressive bone loss.

The integration of digital planning, CBCT-based evaluation, and patient-specific titanium mesh fabrication has expanded the possibilities for management of complex mandibular defects. These technologies allow more accurate treatment planning and may improve control over the final reconstructed ridge morphology⁴³. Nevertheless, successful bone regeneration should not be evaluated only by the amount of newly formed bone. Long-term clinical stability depends on maintenance of regenerated volume, implant function, peri-implant tissue response, and biological adaptation under loading conditions^{44,45}. The current case demonstrated stable clinical and radiographic conditions throughout the follow-up period. No implant failure, peri-implant infection, prosthetic complication, or graft-related instability was observed. Overall, this case supports the use of customized titanium mesh-assisted GBR combined with Bio-Oss® and autogenous bone as a treatment option for severe mandibular ridge deficiencies. The combination of rigid space maintenance, biological enhancement from autogenous bone, and the volume-preserving properties of Bio-Oss® provided suitable conditions for implant-supported rehabilitation.

LIMITATIONS

This report describes a single clinical case; therefore, the findings cannot be generalized to all patients with severe mandibular atrophy.

Although clinical and radiographic outcomes were satisfactory, quantitative volumetric analysis of bone gain was not performed. Three-dimensional measurements using digital imaging methods could provide more detailed information regarding the amount and stability of regenerated bone.

Histological evaluation of the regenerated tissue was also not available; therefore, the exact proportion of newly formed bone, residual graft particles, and connective tissue components could not be determined. Further studies with larger patient groups and longer follow-up periods are required to evaluate the long-term effectiveness of this approach and compare it with other augmentation techniques.

FUTURE DIRECTIONS

Future clinical studies should compare customized CAD/CAM titanium meshes with conventional titanium meshes and alternative regenerative approaches. Additional research is needed to evaluate long-term volumetric stability, patient-reported outcomes, surgical morbidity, and cost-effectiveness of combined grafting protocols. The continued development of digital dentistry, virtual planning, and patient-specific biomaterials may further improve the management of complex alveolar defects and enhance the predictability of reconstructive procedures.

CONCLUSION

Within the limitations of this case report, reconstruction of a severely atrophic mandible using a combination of deproteinized bovine bone mineral (Bio-Oss®) and autogenous bone stabilized with a customized CAD/CAM titanium mesh resulted in adequate bone regeneration and allowed successful implant-supported rehabilitation. The regenerated ridge provided sufficient volume for prosthetically planned implant placement and remained stable during the three-year follow-up period. The combination of autogenous bone, Bio-Oss®, and customized titanium mesh created a stable regenerative environment that supported functional and esthetic rehabilitation in a patient with severe mandibular atrophy.

DECLARATIONS

Competing Interests

The authors declare no conflict of interest.

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None.

Ethical Approval

Informed consent was obtained from patients. Clinical case approved in accordance with ethical standards.

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ORIGINAL ARTICLE

ORAL HEALTH STATUS IN WOMEN WITH PHYSIOLOGICAL PREGNANCY AND TOXICOSIS: A CROSS-SECTIONAL STUDY

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Abstract

Background: Pregnancy represents a unique physiological state characterized by complex neurohumoral and metabolic adaptations that inevitably influence the condition of oral tissues.**Aim:** To evaluate oral health status in women with physiological pregnancy, with particular emphasis on the relationship between early pregnancy toxicosis and oral manifestations during the first half of gestation.**Methods:** A dental examination was performed in 479 pregnant women. From this cohort, 143 women aged 18–45 years with a gestational age of 9–14 weeks were selected for the study and divided into four groups: Group 1 – women with tooth erosion and toxicosis (n=54); Group 2 – women with tooth erosion without toxicosis (n=23); Group 3 – women without tooth erosion but with toxicosis (n=38); and Group 4 – women without tooth erosion or toxicosis (n=28). The prevalence of erosive tooth wear and dental caries, oral hygiene status, gingival inflammation, and salivary pH were assessed. Tooth erosion was evaluated using the Dental Erosion Grading Scale proposed by Eccles and Jenkins (1974), caries experience was assessed according to the International Caries Detection and Assessment System (ICDAS), gingival status was evaluated using the Loe and Silness Gingival Index (1963), and dental plaque accumulation was assessed using the Green and Vermillion Oral Hygiene Index (1964).**Results:** The prevalence of tooth erosion among pregnant women was 16.0%. No statistically significant difference in mean Eccles and Jenkins erosion scores was observed between women with early pregnancy toxicosis and those without toxicosis ($p>0.05$). The combination of tooth erosion and toxicosis was associated with a significantly higher total number of carious lesions and a greater proportion of initial enamel lesions according to ICDAS criteria ($p<0.01$). Salivary pH values were significantly lower in women with erosive tooth lesions compared with those without erosive changes ($p<0.05$). Moderate-to-severe gingivitis and inadequate oral hygiene were observed in all study groups; however, no statistically significant differences were identified between groups ($p>0.05$).**Conclusion:** The findings emphasize the importance of implementing preventive dental programs for pregnant women from the earliest stages of gestation to reduce the risk of erosive tooth wear and dental caries progression, while improving oral hygiene and maintaining periodontal health during pregnancy.**Keywords:** pregnancy toxicosis, tooth erosion, dental caries, gingivitis, salivary pH

INTRODUCTION

Pregnancy represents a unique physiological state characterized by complex neurohumoral and systemic adaptations that inevitably influence the condition of oral tissues. One of the most common complications occurring during the first half of pregnancy is early toxicosis, manifested primarily by nausea and vomiting. Recurrent vomiting results in repeated and prolonged exposure of dental enamel to aggressive acidic gastric contents, which may contribute to enamel

demineralization and the development of erosive tooth lesions¹⁵.

In recent years, the problem of non-carious lesions of dental hard tissues, particularly erosive tooth wear, has gained increasing importance in dentistry. This highlights the need for further investigation of its etiology, pathogenesis, prevalence, as well as effective preventive and therapeutic strategies. Epidemiological studies conducted worldwide have demonstrated the significant influence of socio-behavioral and

environmental factors on the development of oral diseases. Pregnant women represent one of the important risk groups for the occurrence and progression of tooth erosion due to the combination of physiological changes and specific pregnancy-related risk factors^{11,19}.

Erosive tooth wear is defined as a chemical-mechanical process characterized by the progressive and cumulative loss of dental hard tissues without bacterial involvement⁸. In pregnant women, tooth erosion is considered a clinically relevant dental problem associated with the interaction of endogenous factors (hormonal alterations, pregnancy toxicosis, gastroesophageal reflux, and prolonged episodes of vomiting) and exogenous factors (dietary habits, frequent consumption of acidic fruits, and carbonated beverages). During pregnancy, these mechanisms may act simultaneously, emphasizing the importance of detailed medical history assessment for accurate diagnosis and the selection of appropriate preventive and therapeutic measures^{1,21}.

Previous studies have confirmed the relationship between erosive tooth wear and acid-induced demineralization of enamel⁵. Enamel dissolution occurs when the oral environment becomes undersaturated with respect to hydroxyapatite and fluorapatite. This process may be accelerated by exposure to acids originating from dietary sources and gastric reflux. The severity and pattern of erosive damage depend not only on the pH level but also on the chemical characteristics and type of acid involved¹⁸.

Pregnancy-related hormonal changes may also influence dental tissues and contribute to variations in the prevalence and severity of erosive lesions. Among young women, active erosive lesions have been reported in 43% of cases, indicating the importance of early detection and monitoring of this condition during reproductive age, including pregnancy¹⁰.

Behavioral modification remains a key component of successful prevention and requires individualized patient education, motivation, and regular dental follow-up⁷.

Current evidence indicates that pregnant women often receive insufficient dental care. Although the first national consensus statement on oral health care during pregnancy was published in 2012, emphasizing the safety and importance of regular dental care for pregnant women¹⁴, many women continue to

underestimate the importance of maintaining oral health during pregnancy. Recent studies evaluating erosive tooth wear throughout pregnancy have demonstrated an increase in prevalence from 1.5% during the first trimester to 36.4% during the third trimester, with severe enamel loss reported in 7.6% of cases³.

These findings emphasize the necessity of active educational strategies and systematic assessment of risk factors, including tooth erosion, which may significantly affect the quality of life of women during pregnancy⁴.

Despite the clear pathophysiological relationship between early toxicosis and acid-related dental tissue damage, the prevalence, severity, and clinical characteristics of tooth erosion in pregnant women with this obstetric condition remain insufficiently investigated. Most available studies primarily focus on periodontal inflammatory diseases and dental caries, while erosive tooth wear has received comparatively less attention. The influence of early toxicosis on salivary buffering capacity, oral hygiene status, and the development of clinical management strategies for pregnant women with erosive lesions require further investigation. The above-mentioned considerations highlight the medical and social importance of studying oral health conditions in women with physiological pregnancy and pregnancy-associated toxicosis. Early identification of risk factors and clinical manifestations during the first trimester may contribute to the development of evidence-based, individualized preventive approaches aimed at maintaining oral health and reducing the risk of dental diseases in pregnant women.

The aim of this study was to evaluate the oral health status of pregnant women with physiological pregnancy and early pregnancy toxicosis during the first half of gestation.

METHODS

A dental examination was conducted among 479 pregnant women at the Obstetrics and Gynecology Department Clinic of the Russian University of Medicine. From this cohort, 143 women were selected to participate in the cross-sectional study according to the following inclusion criteria:

- pregnant women aged 18–45 years;
- gestational age of 9–14 weeks;
- voluntary agreement to participate in the study and provision of written informed consent.

The following exclusion criteria were applied:

- pregnant women younger than 18 years or older than 45 years;
- gestational age less than 9 weeks or more than 14 weeks;
- decompensated somatic diseases;
- malignant neoplasms of the oral cavity;
- psychoneurological disorders interfering with participation in the study.

The presence of tooth erosion and early pregnancy toxicosis was assessed during the dental and medical examination. Early pregnancy toxicosis was diagnosed by obstetricians and gynecologists at the University Clinic according to clinical criteria corresponding to ICD-10 code O21.0 (mild hyperemesis gravidarum).

Women with a gestational age exceeding 14 weeks at the time of dental examination were excluded from the study (n=336).

All participants were informed about the objectives and procedures of the study and provided written informed consent prior to participation. The study protocol was reviewed and approved by the University Ethics Committee.

Based on the presence or absence of tooth erosion and early pregnancy toxicosis, the 143 enrolled women were divided into four study groups:

- Group 1 (n=54) – women with tooth erosion and early pregnancy toxicosis;
- Group 2 (n=23) – women with tooth erosion without early pregnancy toxicosis;
- Group 3 (n=38) – women without tooth erosion but with early pregnancy toxicosis;
- Group 4 (n=28) – women without tooth erosion or early pregnancy toxicosis.

The dental examination included assessment of erosive tooth wear using the Dental Erosion Grading Scale proposed by Eccles and Jenkins (1974). The scoring criteria were as follows: 0 – absence of erosion; 1 – erosion limited to enamel; 2 – dentin involvement affecting less than one-third of the lesion surface; 3 – dentin involvement affecting more than one-third of the lesion surface. Dental caries lesions were assessed using the International Caries Detection and Assessment System (ICDAS, 2002) according to the following criteria: 0 – sound tooth surface; 1 – first visual change in enamel visible only after air drying; 2

– distinct visual change in enamel visible without air drying; 3 – localized enamel breakdown; 4 – underlying dark shadow from dentin; 5 – distinct cavity with visible dentin; 6 – extensive distinct cavity with visible dentin.

The level of oral hygiene was evaluated using the Simplified Oral Hygiene Index (OHI-S) developed by Green and Vermillion (1964). Gingival inflammation was assessed using the Gingival Index (GI) proposed by Loe and Silness (1963).

The pH of mixed saliva samples was measured using diagnostic indicator strips (pH Scan, Russia). Participants were instructed to refrain from eating for 1.5–2 hours before the examination. Prior to saliva collection, they rinsed their mouth with distilled water. Three saliva samples were collected from each participant, and the mean pH value was calculated.

Statistical analyses were performed using Statistica 7.0 (StatSoft, USA) and Microsoft Excel 2016 (Microsoft Corporation, USA). For intergroup comparisons of mean oral health indicators, an independent-samples t-test (Student's t-test) was applied. Differences were considered statistically significant at $p < 0.05$, which corresponds to the conventional significance threshold used in biomedical research.

RESULTS

A dental examination of 479 pregnant women revealed erosive tooth wear in 77 women, with an overall prevalence of 16%. Tooth erosion was diagnosed in 54 (70%) women whose pregnancy was complicated by early toxicosis and in 23 (30%) women with a physiological course of pregnancy. The mean number of teeth affected by erosion was 7.82 ± 0.30 . Dental hypersensitivity was reported by 53% of pregnant women with tooth erosion, while esthetic concerns were reported by 16% of these women.

The mean Eccles and Jenkins score in pregnant women with toxicosis (Group 1) was 7.91 ± 0.41 . Erosive lesions with score 1 accounted for 5.74 ± 0.26 , while the corresponding values for score 2 and score 3 were 2.06 ± 0.20 and 0.11 ± 0.06 , respectively. The mean Eccles and Jenkins score in pregnant women without signs of toxicosis (Group 2) was 7.61 ± 0.37 . In this group, erosive lesions with score 1 accounted for 5.35 ± 0.37 , while the corresponding values for score 2 and score 3 were 2.09 ± 0.27 and 0.17 ± 0.10 , respectively (Figure 1).

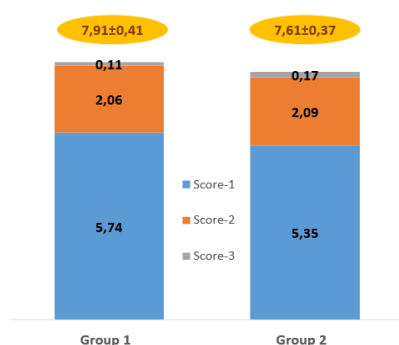


Figure 1. The distribution of erosive tooth wear severity in pregnant women according to the Dental Erosion Grading Scale (Eccles and Jenkins, 1974).

The differences in Eccles and Jenkins scores between women with early toxicosis and those without toxicosis were not statistically significant ($p>0.05$).

The analysis of caries experience according to ICDAS criteria demonstrated a predominance of initial enamel carious lesions (codes D1 and D2) across all study groups.

The mean ICDAS value in pregnant women from Group 1 was 6.89 ± 0.35 . The mean number of initial carious lesions (D1, D2) was 3.79 ± 0.25 (55.5%); D3 and D4 lesions accounted for 1.79 ± 0.14 (26.2%), while D5 and D6 lesions accounted for 1.31 ± 0.19 (19.2%). The mean ICDAS value in Group 2 was 6.18 ± 0.44 . The number of teeth with D1 and D2 lesions was 3.26 ± 0.29 (52.8%), D3 and D4 lesions accounted for 2.09 ± 0.23 (33.9%), and D5 and D6 lesions accounted for 0.83 ± 0.18 (13.5%).

The mean ICDAS value among pregnant women without tooth erosion in Group 3 was 5.58 ± 0.33 . The proportion of initial enamel caries (D1, D2) was 48.8% (2.79 ± 0.27), D3 and D4 lesions accounted for 32.2% (1.84 ± 0.15), and D5 and D6 lesions accounted for 16.6% (0.95 ± 0.14). The mean ICDAS value in Group 4 was 6.06 ± 0.49 . The mean number of D1 and D2 lesions was 2.89 ± 0.25 (47.8%), D3 and D4 lesions accounted for 2.82 ± 0.33 (46.7%), and D5 and D6 lesions accounted for 0.35 ± 0.13 (5.8%).

The analysis of differences between groups demonstrated that pregnant women in Group 1 had a significantly higher total number of carious lesions, as well as a significantly higher number of initial enamel lesions (D1, D2), compared with Groups 3 and 4 ($p<0.01$). The number of dentin cavities (D5, D6) in pregnant women in Group 4 was significantly lower

than that observed in pregnant women from Groups 1 ($p<0.001$), 2 ($p<0.01$), and 3 ($p<0.01$) (Figure 2).

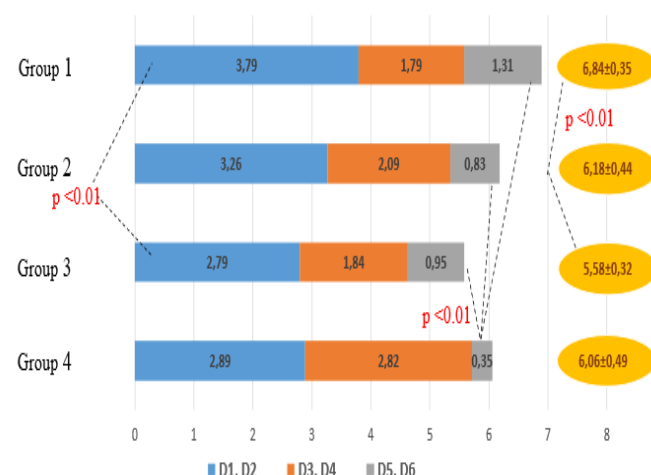


Figure 2. Caries experience in pregnant women according to ICDAS criteria

Dental examinations revealed substantial dental plaque accumulation among all examined pregnant women. Oral Hygiene Index (OHI-S) values did not differ significantly between the study groups. The mean OHI-S value was 1.76 ± 0.10 in Group 1, 1.72 ± 0.16 in Group 2, 1.75 ± 0.13 in Group 3, and 1.94 ± 0.18 in Group 4 ($p>0.05$) (Figure 3).

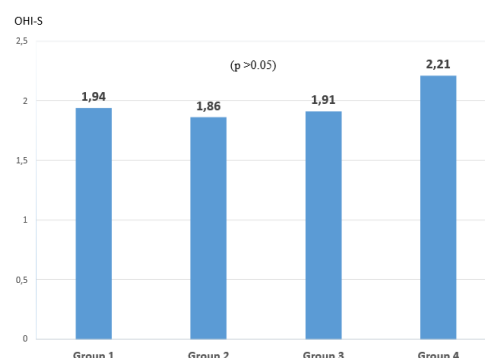


Figure 3. Oral Hygiene Index (Green and Vermillion, 1964) values in pregnant women.

Periodontal tissue examination in pregnant women revealed signs of gingival inflammation, including marginal gingival hyperemia, swelling of the gingival papillae, and bleeding on probing, indicating impaired periodontal status during the first half of gestation.

The mean Gingival Index (GI) value was 1.95 ± 0.19 in Group 1, 1.86 ± 0.13 in Group 2, and 1.91 ± 0.12 in Group 3, corresponding to moderate gingivitis. In Group 4, the

mean GI value was higher (2.21 ± 0.12), corresponding to severe gingivitis. No statistically significant differences in GI values were observed among the study groups ($p > 0.05$) (Figure 4).

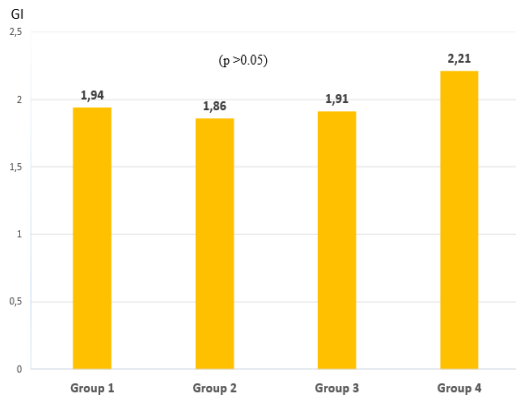


Figure 4. Gingival Index (Loe and Silness, 1963) values in pregnant women

Analysis of mixed saliva samples from pregnant women demonstrated a shift in salivary pH toward the acidic range, with an overall mean value of 6.27 ± 0.05 .

The mean salivary pH value in pregnant women with tooth erosion was 6.08 ± 0.05 in Group 1 and 6.30 ± 0.09 in Group 2 ($p > 0.05$). Among pregnant women without erosive lesions, salivary pH values were significantly higher, reaching 6.82 ± 0.07 in Group 3 and 6.87 ± 0.09 in Group 4 ($p < 0.01$) (Figure 5)

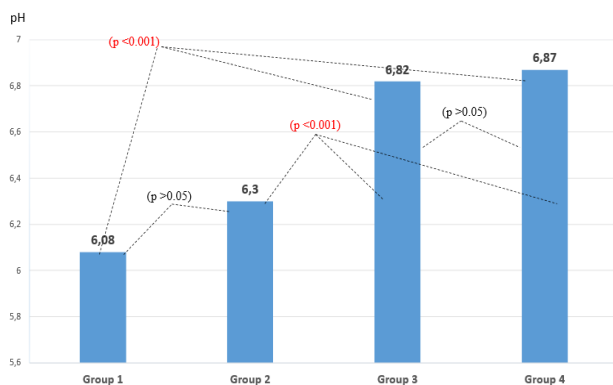


Figure 5. Salivary pH values in pregnant women

The lowest mixed salivary pH value (5.62 ± 0.06) was observed in pregnant women with tooth erosion who reported vomiting as a symptom of early toxicosis. Among women reporting sour eructation and nausea, the mean salivary pH value was 6.08 ± 0.04 , while in women with a physiological course of pregnancy, it was 6.47 ± 0.08 ($p < 0.001$).

A similar tendency was observed among pregnant women with early toxicosis without tooth erosion; however, salivary pH values under the same clinical symptoms were significantly higher (6.13 ± 0.14 , 6.59 ± 0.08 , and 7.02 ± 0.05 , respectively; $p < 0.001$).

DISCUSSION

The present study investigated oral health status in women with physiological pregnancy and those with early pregnancy toxicosis, with particular emphasis on erosive tooth wear, dental caries, oral hygiene status, gingival inflammation, and salivary pH. The findings revealed several clinically relevant associations between symptoms of early toxicosis and pathological changes in dental hard tissues and periodontal tissues.

Prevalence and severity of tooth erosion

The prevalence of tooth erosion in the examined cohort was 16%, which is consistent with previously reported data from European populations. Jaeggi and Lussi [10] demonstrated that the prevalence of erosive tooth wear varies considerably (from 5% to 80%) depending on age, geographical region, and diagnostic criteria. The prevalence observed in our study falls within the lower range of previously reported values, which may be explained by the relatively young age of participants and the absence of severe systemic comorbidities.

The mean Eccles and Jenkins scores did not differ significantly between women with early pregnancy toxicosis (Group 1: 7.91 ± 0.41) and those without toxicosis (Group 2: 7.61 ± 0.37 ; $p > 0.05$). These findings suggest that although early pregnancy toxicosis is a recognized risk factor for erosive tooth wear^{2,13}, the severity of existing erosive lesions may be influenced more strongly by chronic pre-existing factors, such as dietary habits, oral health behavior, and baseline salivary buffering capacity, rather than by the acute episodes of vomiting and gastric acid exposure occurring during the first half of gestation.

The findings indicate that the combination of pregnancy toxicosis and dietary habits may have a greater influence on the progression of erosive tooth wear in pregnant women.

This interpretation is supported by the observation that score-1 lesions (enamel-only involvement) predominated in both groups, accounting for approximately 70–73% of erosive defects, whereas score-3 lesions (dentin involvement affecting more than

one-third of the lesion surface) were uncommon (<2%). Such a distribution suggests that erosive tooth wear in most pregnant women is identified at an early stage, emphasizing the importance of timely preventive measures.

A recent prospective observational study highlighted that hormonal fluctuations during pregnancy, particularly increased progesterone and estrogen levels, may play an important role in maintaining stomatognathic health, while the frequency of vomiting itself was not identified as an independent significant factor. This observation is consistent with our findings that the severity of erosive lesions did not differ significantly between women with and without toxicosis, suggesting that chronic hormonal and behavioral factors may have a greater influence than short-term vomiting episodes ¹⁷.

Dental caries and its association with tooth erosion and pregnancy toxicosis

A key finding of this study was that pregnant women in Group 1 (tooth erosion and early pregnancy toxicosis) had a significantly higher total number of carious lesions compared with women in Groups 3 and 4 ($p<0.01$). The number of initial enamel carious lesions (ICDAS codes D1 and D2) was also significantly higher in Group 1. These findings support the hypothesis that acid-induced enamel demineralization caused by gastric reflux and vomiting may create favorable conditions for the development and progression of cariogenic processes.

Although erosive tooth wear and dental caries have different etiological mechanisms, with erosion being primarily a chemical process and caries being associated with bacterial activity, repeated exposure to gastric acids may weaken the enamel surface and increase its susceptibility to subsequent bacterial acid challenges ^{5,16}.

The lowest prevalence of dentin cavities (D5, D6) was observed in Group 4 (women without tooth erosion or toxicosis), which was expected due to the absence of both major risk factors. However, Group 3 (women with toxicosis without tooth erosion) demonstrated an intermediate pattern. In this group, initial carious lesions (D1, D2) accounted for 48.8%, while dentin cavities (D5, D6) accounted for 16.6%.

These findings suggest that early pregnancy toxicosis alone, even in the absence of clinically detectable

erosive tooth wear, may contribute to the progression of dental caries, possibly through alterations in salivary pH and reduced buffering capacity.

Oral hygiene and periodontal status

Among pregnant women from all study groups, Gingival Index (GI) values ranged from 1.86 to 2.21, with no statistically significant differences between groups. These findings are consistent with the well-established increase in gingival inflammation during pregnancy, which is associated with elevated levels of progesterone and estrogen. These hormonal changes may increase vascular permeability and enhance the inflammatory response of gingival tissues to dental plaque accumulation.

The absence of significant differences between women with and without early pregnancy toxicosis indicates that toxicosis itself does not appear to substantially increase gingival inflammation beyond the effects of pregnancy-related hormonal changes.

Oral hygiene status, assessed using the OHI-S index, demonstrated insufficient plaque control across all study groups, with values ranging from 1.72 to 1.94. Inadequate oral hygiene likely contributed to the increased prevalence of dental caries and the pronounced gingival inflammatory changes observed among the examined pregnant women. Interestingly, Group 4 (women with physiological pregnancy without erosion or toxicosis) demonstrated the highest OHI-S value (1.94 ± 0.18) and the highest GI value (2.21 ± 0.12).

This finding may be explained by the possibility that women with an apparently uncomplicated pregnancy and without noticeable dental symptoms may underestimate their oral health risks and therefore demonstrate lower motivation toward preventive oral care.

Salivary pH and pregnancy toxicosis

The most pronounced differences between the study groups were observed in salivary pH values. Pregnant women with tooth erosion (Groups 1 and 2) demonstrated significantly lower salivary pH values (6.08–6.30) compared with women without erosive lesions (6.82–6.87) ($p<0.05$). These findings are consistent with the established role of reduced salivary pH in the demineralization process associated with erosive tooth wear ²¹.

Among women with early pregnancy toxikosis, the severity of clinical symptoms demonstrated an inverse association with salivary pH values. The lowest pH value (5.62 ± 0.06) was observed in women with tooth erosion who experienced vomiting, followed by women with sour eructation and nausea (6.08 ± 0.04), while the highest pH value (6.47 ± 0.08) was observed in women with a physiological course of pregnancy.

A similar gradient was observed among women with toxikosis without tooth erosion; however, the absolute pH values were significantly higher at each symptom level ($p < 0.001$). These findings indicate that symptoms associated with early toxikosis may contribute to a reduction in salivary pH, while the presence of established erosive lesions is associated with an even more acidic oral environment, possibly due to the combined effects of reduced buffering capacity and continuous acid-mediated enamel demineralization.

Our findings are consistent with a large recent study demonstrating a significant gradual decrease in unstimulated salivary pH from the first to the third trimester of pregnancy, reflecting a shift toward a more acidic oral environment compared with non-pregnant controls²⁰. Lussi et al. emphasized the importance of salivary pH and buffering capacity in the pathogenesis of erosive tooth wear, which is directly supported by the observations of the present study¹³.

Bartlett et al. reported an association between dietary habits and erosive tooth wear in adults; however, our findings extend previous knowledge by demonstrating that pregnancy-specific factors, particularly symptoms of early toxikosis, may influence salivary pH changes during gestation².

Clinical and preventive implications

Unlike previous studies that have primarily focused on periodontal diseases during pregnancy, the present study highlights the importance of non-carious dental hard tissue lesions as an additional oral health concern in this population.

The findings have several important practical implications for dental care in pregnant women. First, the high prevalence of early-stage erosive lesions (score-1) indicates that screening for tooth erosion should be incorporated into routine dental examinations during the first trimester of pregnancy, particularly among women reporting vomiting or symptoms of gastric acid reflux.

Second, the increased risk of dental caries observed in women with both tooth erosion and early pregnancy toxikosis suggests that these patients may benefit from intensified preventive strategies, including topical fluoride applications, remineralizing agents, and individualized dietary counseling⁹.

The presence of inadequate oral hygiene and gingival inflammation across all study groups emphasizes the need for oral health education, professional teeth cleaning, and effective plaque control as essential components of prenatal healthcare. Furthermore, salivary pH assessment may represent a simple and non-invasive approach for identifying pregnant women at increased risk of erosive tooth wear and dental caries.

Limitations of the study

The cross-sectional design of the study allows the identification of associations between early pregnancy toxikosis symptoms and oral health status; however, the findings are limited to the first trimester of gestation. Nevertheless, this initial assessment was necessary to obtain baseline data for the development and implementation of a preventive program for the examined pregnant women.

Longitudinal follow-up was not included in the present stage of the study; however, it will be presented as the second part of the larger research project during the evaluation of the implemented prevention program.

A detailed dietary assessment, including the evaluation of acidogenic food and beverage consumption and other important potential confounding risk factors, was not included in this manuscript. However, these factors were assessed and will be presented as part of the broader research project¹².

Salivary flow rate measurements were not performed in this study; only salivary pH values were evaluated.

Despite the single-center design, this study provides clinically relevant observations and emphasizes the need for future prospective multicenter investigations using standardized diagnostic and methodological protocols.

Prospective cohort studies and preventive intervention trials

The present article represents the first stage of a larger

study aimed at comparing oral health status among women with physiological pregnancy and those experiencing early pregnancy toxicosis.

In addition to clinical dental examinations, a questionnaire survey was conducted among pregnant women using a modified version of the WHO (2013) Oral Health Questionnaire for Adults. Based on the obtained data, correlation analysis was performed to identify the most relevant risk factors, including dietary characteristics and oral health-related behaviors, influencing the severity of erosive tooth lesions.

All pregnant women diagnosed with tooth erosion were subsequently included in a preventive program consisting of oral health education, professional plaque removal, dietary recommendations, and topical application of remineralizing agents. Follow-up visits were scheduled at different gestational stages according to individual risk assessment.

Monitoring continued throughout pregnancy and the postpartum period, with the final evaluation of oral health status planned 9 months after initiation of the preventive program.

CONCLUSION

Tooth erosion was identified in women with both early pregnancy toxicosis and physiological pregnancy. The severity of erosive tooth wear did not differ significantly between pregnant women with early toxicosis and those without toxicosis.

The combination of early pregnancy toxicosis and dietary factors, including increased consumption of acidic foods and beverages, may contribute to a higher rate of progression and greater severity of erosive tooth wear among pregnant women. Pregnant women with both toxicosis and tooth erosion demonstrated a significantly higher total number of carious lesions and a greater proportion of initial enamel lesions.

The presence of toxicosis symptoms was associated with a shift in salivary pH toward the acidic range, with significantly lower salivary pH values observed in pregnant women with tooth erosion compared with women without erosive lesions but with similar toxicosis symptoms.

Signs of gingival inflammation were observed among all study participants, indicating the presence of pregnancy-associated periodontal changes.

The findings of this study emphasize the importance of implementing preventive oral health programs for pregnant women from the earliest stages of gestation to prevent or reduce the progression of erosive tooth wear and dental caries, while improving oral hygiene and maintaining periodontal health.

DECLARATIONS

Competing Interests

The author declare no conflict of interest.

Funding

No external funding was received for this study.

Ethical Approval

The study was reviewed and approved by University Ethical Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Consent for publication

Patients were informed verbally and in writing about the study and gave written informed consent.

Availability of data and materials

Not availability

Clinical trial number

Not applicable

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